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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	030206.0239.UTL1	*Total Pages*	142
First Named Inventor or Application Identifier			
Bharat Chowrira, et al.			
Express Mail Label No.	EL676079877US		

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Robert W. Prince

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

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1. ☐ Fee Transmittal Form *(Submit an original, and a duplicate for fee processing)*
2. ☒ Specification [*Total Pages* 133] *(preferred arrangement set forth below)*
   - Descriptive title of the Invention
   - Cross References to Related Applications
   - Statement Regarding Fed sponsored R & D
   - Reference to Microfiche Appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings *(if filed)*
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure
3. ☒ Drawing(s) *(35 USC 113)* [*Total Sheets* 4]
4. ☐ Oath or Declaration [*Total Pages* ☐]
   a. ☐ Newly executed (original or copy)
   b. ☐ Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional with Box 17 completed)* ***[Note Box 5 below]***
      i. ☐ DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b)
5. ☐ Incorporation By Reference *(useable if Box 4b is checked)* The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
6. ☐ Microfiche Computer Program *(Appendix)*
7. Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all necessary)*
   a. ☐ Computer Readable Copy
   b. ☐ Paper Copy (identical to computer copy)
   c. ☐ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

8. ☐ Assignment Papers (cover sheet & document(s))
9. ☐ 37 CFR 3.73(b) Statement ☐ Power of Attorney *(when there is an assignee)*
10. ☐ English Translation Document *(if applicable)*
11. ☐ Information Disclosure Statement (IDS)/PTO-1449 and Form 892 ☐ Copies of IDS Citations. Per Rule 97(d) copies of those documents are not provided.
12. ☒ Preliminary Amendment
13. ☒ Return Receipt Postcard (MPEP 503) *(Should be specifically itemized)*
14. ☒ Small Entity Statement(s) ☐ Statement filed in prior application, Status still proper and desired
15. ☐ Certified Copy of Priority Document(s) *(if foreign priority is claimed)*
16. * ☐ .....

17. If a CONTINUING APPLICATION, *check appropriate box and supply the requisite information:*

☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No:

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The filing fee has been calculated as follows:

FOR	NUMBER FILED	NUMBER EXTRA	RATE	CALCULATIONS
TOTAL CLAIMS	48 -20 =	28	x $18.00	$504.00
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MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $260.00	$260.00
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Dated:

Respectfully submitted,

By: _____
Robert W. Prince
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant or Patentee:	**Bharat M. Chowrira et al.**
Serial No.:	**(not yet assigned)**
Filed:	**April 15, 2000**
Entitled:	**METHOD AND REAGENT FOR THE INHIBITION OF TELOMERASE ENZYME**
Attorney Docket No.:	**3880/87530**

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(d) AND 1.27(d)) -SMALL BUSINESS CONCERN

I hereby declare that I am an official empowered to act on behalf of the small business concern identified below:

Name of Organization: Ribozyme Pharmaceuticals Inc.

Address of Organization: 2950 Wilderness Place, Boulder, CO

I hereby declare that the small business concern identified above qualifies as a small business concern as defined in 37 C.F.R. § 1.9(d) for purposes of paying reduced fees under § 41(a) and (b) of Title 35, United States Code, with regard to the invention entitled

METHOD AND REAGENT FOR THE INHIBITION OF TELOMERASE ENZYME

by inventor(s) Bharat M. Chowrira, James McSwiggen and Dan T. Stinchcomb
described in

[X] the specification filed herewith
[ ] Application Serial No. _____, filed _____.
[ ] Patent No. _____, issued _____.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern with regard to the above-identified invention.

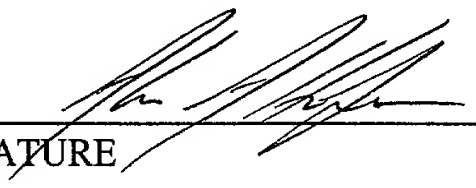
If the rights held by the above identified small business concern are not exclusive, each individual concern or organization having rights in the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who would not qualify as an independent inventor under 37 CFR § 1.9(c) if

that person made the invention, or by any concern which would not qualify as a small business concern under 37 CFR § 1.9(d), or a nonprofit organization under 37 CFR § 1.9(e).

Alene Holzman
NAME OF PERSON SIGNING

Vice President of Business Development
TITLE IN ORGANIZATION

2950 Wilderness Place, Boulder, CO 80301
ADDRESS



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4/24/00

DATE

UTILITY APPLICATION

UNDER 37 CFR § 1.53(B) (2)

TITLE: METHOD AND REAGENT FOR THE INHIBITION OF TELOMERASE ENZYME

APPLICANT (S): Bharat M. Chowrira, James McSwiggen, Dan T. Stinchcomb

Correspondence Enclosed:

Utility Transmittal (2 pgs); Specification (129 pgs); Claims (3 pgs); Abstract (1 pg); Drawings (4 pgs); Small Entity Statement (2 pg); Preliminary Amendment (2 pgs); Check No. 503525 in the Amount of $766.00; and Return Postcard

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Robert W. Prince

DESCRIPTION

METHOD AND REAGENT FOR THE INHIBITION OF TELOMERASE ENZYME

Background Of The Invention

The present invention concerns compounds, compositions, and methods for the study, diagnosis, and treatment of conditions and diseases related to the level of telomerase enzyme.

The following is a brief description of the current understanding in the biology of telomerase and its components. The discussion is not meant to be complete and is provided only for understanding of the invention that follows. The summary is not an admission that any of the work described below is prior art to the claimed invention.

The ribonucleoprotein enzyme telomerase consists of an RNA template subunit and one or more protein subunits including telomerase reverse transcriptase (TERT), which function together to direct the synthesis of telomeres. Telomeres exist as non-nucleosome DNA/protein complexes at the physical ends of eukaryotic chromosomes. These capping structures maintain chromosome stability and replicative potential (Zakian, V. A., 1995, Science, 270, 1601-1607). Telomere structure is characterized by tandem repeats of conserved DNA sequences rich in G-C base pairs. Additional conserved telomere elements include a terminal 3'-overhang in the G-rich strand and non-histone structural proteins that are complexed with telomeric DNA in the nucleus. (Blackburn, "E., 1990, JBC., 265, 5919-5921.). Observed shortening of telomeres coincides with the onset of cellular senescence in most somatic cell lines lacking significant levels of telomerase. This finding has had a profound impact on our views concerning the mechanisms of aging, age related disease, and cancer.

Conventional DNA polymerases are unable to fully replicate the ends of linear chromosomes (Watson, J. D., 1972, Nature, 239, 197-201). This inability stems from the 3' G-rich overhang that is a product of ribonuclease cleavage of the RNA primer used in DNA replication. The overhang prevents DNA polymerase replication since the recessed C-rich parent strand cannot be used as a template. Telomerase overcomes this limitation by extending the 3' end of the chromosome using deoxyribonucleotides as substrates and a sequence within the telomerase RNA subunit as a template. (Lingner,

J., 1995, Science, 269, 1533-1534). As such, telomerase is considered a reverse transcriptase that is responsible for telomere maintenance.

Telomerase was first discovered by in *Tetrahymena thermophila* in 1985 (Greider, C. W., 1995, Cell, 43, 405-413). The RNA subunits and their respective genes were later discovered and characterized in protozoa, budding yeast, and mammals. Genetic studies of these genes confirmed the role of telomerase RNA (TR) in determining telomere sequence by mutating genes which encode the telomeric RNA (Yu, G. L., 1990, Nature, 344, 126-132), (Singer, M. S., 1994, Science, 266, 404-409), (Blasco, M. A., 1995, Science, 269, 1267-1270). These studies showed that telomerase activity parallels TR expression in protozoa, yeast and mice. However, the expression of human telomerase RNA (hTR) does not correlate well with telomerase activity in mammalian cells. Many human tissues express hTR but are devoid of telomerase activity (Feng, J., 1995, Science, 269, 1236-1241). Knockout mice, in which the mTR gene has been deleted from germline cells, have been shown to be viable for at least six generations. Cells from later generations of these mice showed chromosomal abnormalities consistent with telomere degradation, indicating that mTR is necessary for telomere length maintenance, but is not required for embryonic development, oncogenic transformation, or tumor formation in mice (Blasco, M. A., 1997, Cell, 91, 25-34).

The first catalytically active subunit of telomerase (p123) was isolated from *Euplotes aediculatus* along with another subunit (p43) and a 66-kD RNA subunit (Linger, J., 1996, Proc. Natl. Acad. Sci., 93, 10712-10717). Subsequent studies revealed telomerase catalytic subunit homologs from fission yeast (Est2p) and human genes (TRT1). The human homolog, TRT1 encoding hTERT, expressed mRNA with a strong correlation to telomerase activity in human cells (Nakamura, T. M., 1997, Science, 277, 955-959). Reconstitution of telomerase activity with *in vitro* transcribed and translated hTERT and hTR, either co-synthesized or simply mixed, demonstrated that hTERT and hTR represent the minimal components of telomerase. Furthermore, transient expression of hTERT in normal diploid human cells restored telomerase activity, demonstrating that hTERT is the only component necessary to restore telomerase activity in normal human cells (Weinrich, S. L., 1997, Nature Genetics, 17, 498-502). The introduction of telomerase into normal human cells using hTERT expression via transfection has resulted in the extension of life span in these cells. Such findings indicate that telomere loss in the absence of telomerase is the "mitotic clock"

that controls the replicative potential of a cell prior to senescence (Bodnar, A. G., 1998, Science, 279, 349-352).

Expression of telomerase is observed in germ cell and most cancer cell lines. These "immortal" cell lines continue to divide without shortening of their telomeres (Kim, N. W., 1994, Science, 266, 2011-2015). A model of tumor progression has evolved from these findings, suggesting a role for telomerase expression in malignant transformation. Successful malignant transformation in human cells was accomplished for the first time by ectopic expression of hTERT in combination with two oncogenes, SV40 large-T and H-ras. Injection of nude mice with cells expressing these oncogenes and hTERT resulted in rapid growth of tumors. These observations indicate that hTERT mediated telomere maintenance is essential for the formation of human tumor cells (Hahn, W. C., 1999, Nature, 400, 464-468).

Various methods have been developed to assay telomerase activity *in vitro*. The most widely used method to characterize telomerase activity is the telomeric repeat amplification protocol (TRAP). TRAP utilizes RT-PCR of cellular extracts to measure telomerase activity by making the amount of PCR target dependant upon the biochemical activity of the enzyme (Kim, N. W., 1997, Nucleic Acids Research, 25, 2595-2597).

A variety of animal models have been designed to assay telomerase activity *in vivo*. Inhibition of telomerase activity has been analyzed in rats via cell proliferation studies with MNU (N-methyl-N-nitosurea) induced mammary carcinomas in response to treatment with 4-(hydroxyphenyl)retinamide (4-HPR), a known inhibitor of mammary carcinogenesis in animal models and premenopausal women (Bednarek, A., 1999, Carcinogenesis, 20, 879-883). Additional studies have focused on the up-regulation of telomerase in transformed cell lines from animal and human model systems (Zhang, P. B., 1998, Leuk. Res., 22, 509-516), (Chadeneau, C., 1995, Oncogene, 11, 893-898), (Greenberg, R., 1999, Oncogene, 18, 1219-1226).

Human cell culture studies have been established to assay inhibition of telomerase activity in human carcinomas responding to various therapeutics. A human breast cancer model for studying telomerase inhibitors is described (Raymond, E., 1999, Br. J. Cancer, 80, 1332-1341). Human studies of telomerase expression as related to various other cancers are described including cervical cancer (Nakano, K., 1998, Am. J. Pathol,

153, 857-864), endometrial cancer (Kyo, S., 1999, Int. J. Cancer, 80, 60-63), meningeal carcinoma (Kleinschmidt-DeMasters, B. K., 1998, J. Neurol. Sci., 161, 124-134), lung carcinoma (Yashima, K., 1997, Cancer Reseach, 57, 2372-2377), testicular cancer in response to cisplatin (Burger, A. M., 1997, Eur. J. Cancer, 33, 638-644), and ovarian carcinoma (Counter, C. M., 1994, Proc. Natl. Acad. Sci., 91, 2900-2904).

Particular degenerative and disease states that can be associated with telomerase expression modulation include but are not limited to:

- Cancer: Almost all human tumors have detectable telomerase activity (Shay, J. W., 1997, Eur. J. Cancer, 33, 787-791). Treatment with telomerase inhibitors may provide effective cancer therapy with minimal side effects in normal somatic cells that lack telomerase activity. The therapeutic potential exists for the treatment of a wide variety of cancer types.

- Restinosis: Telomerase inhibition in vascular smooth muscle cells may inhibit restinosis by limiting proliferation of these cells.

- Infectious disease: Telomerase inhibition in infectious cell types that express telomerase activity may provide selective anti-infectious agent activity. Such treatment may prove especially effective in protozoan-based infection such as Giardia and Lesh Meniesis.

- Transplant rejection: Telomerase inhibition in endothelial cell types may demonstrate selective immunnosuppressant activity. Activation of telomerase in transplant cells could benefit grafting success through increased proliferative potential.

- Autoimmune disease: Telomerase modulation in various immune cells may prove beneficial in treating diseases such as multiple sclerosis, lupus, and AIDS.

- Age related disease: Activation of telomerase expression in cells at or nearing senescence as a result of advanced age or premature aging could benefit conditions such as macular degeneration, skin ulceration, and rheumatoid arthritis.

The present body of knowledge in telomerase research indicates the need for methods to assay telomerase activity and for compounds that can regulate telomerase expression for research, diagnostic, trait alteration, animal health and therapeutic use.

Gaeta *et al.,* US patents No. 5,760,062; 5,767,278; 5,770,613 have described small molecule inhibitors of human telomerase RNA (hTR) subunit.

Blasco *et al.,* 1995, Science, 269, 1267-1270 describe the synthesis and testing of antisense oligonucleotides targeted against a specific region of the mouse telomerase RNA (mTR) subunit and reported reduction in telomerase activity in mice.

Bisoffi *et al.,* 1998, Eur. J. Cancer, 34, 1242-1249 have studied the down regulation of human telomerase activity by a retrovirus vector expressing antisense RNA targeted against the hTR RNA.

Norton *et al.,* 1996, Nature Biotechnology, 14, 615-619 have reported the use of a peptide nucleic acid (PNA) molecule targeting hTR RNA to down regulate telomerase activity in human immortal breast epithelial cells.

Yokoyama *et al.,* 1998, Cancer Research, 58, 5406-5410 have reported the synthesis and testing of hammerhead ribozyme constructs targeting hTR RNA resulting in a decrease in the telomerase activity in Ishikawa cells.

Henderson, European Patent Application No. 666,313-A2 describes methods of identifying and cloning hTR gene for use in gene therapy approaches for creating aberrant telomeric sequences in transfected human tumor cells. A ribozyme based gene therapy approach to inhibit the expression of hTR gene is described as well. The intended result of such therapies involves incurred genetic instability based on non-native telomeric sequences resulting in rapid cell death of the treated cells.

West *et al.,* US patent No. 5,489,508 describe methods for determining telomere length and telomerase activity in cells. Inhibitors of hTR RNA, including oligonucleotides and/or small molecules are described.

These foregoing approaches of targeting the telomerase RNA subunit (TR) may not be very beneficial, because as demonstrated by Feng *et al.*, (Feng, J., 1995, Science, 269, 1236-1241), telomerase activity in humans does not correlate well to hTR concentration.

Collins *et al.,* International PCT publication No. WO 98/01542 describes assays for the detection of telomerase activity. Four human telomerase subunit proteins are described called p140, p105, p48 and p43. In addition, hybridization probes and primers are described as inhibitors of telomerase gene function. Antibody based inhibitors of telomerase protein subunits are described.

A more attractive approach to telomerase regulation would involve the regulation of human telomerase by modulating the expression of the protein subunits of the enzyme, preferably the reverse transcriptase (hTERT) subunit. Based of reconstitution experiments, hTERT and hTR represent the minimal components of telomerase. Since hTR expression does not correlate well with telomerase activity in human cells and since many human cells express hTR without telomerase activity, targeting hTERT may prove more beneficial than targeting hTR. hTERT is the only component necessary to restore telomerase activity in normal human cells. A study in which the three major subunits of telomerase (hTR, TP1, and hTERT were assayed in normal and malignant endometrial tissues determined that hTERT is a rate limiting determinant of enzymatic activity of human telomerase (Kyo, S., 1999, Int. J. Cancer, 80, 60-63). Additional protein subunits that have been isolated most likely serve only a structural role in telomerase activity, but may be important in enhancing the activity of the telomerase enzyme. As such, hTERT is one of the better targets for the ectopic regulation of telomerase activity.

Cech *et al.,* International PCT publication No. WO 98/14593 describe compositions and methods related to hTERT for diagnosis, prognosis and treatment of human diseases, for altering proliferative capacity in cells and organisms, and for screening compounds and treatments with potential use as human therapeutics.

Cech *et al.,* International PCT publication No. WO 98/14592 describe nucleic acid and amino acid sequences encoding various telomerase protein subunits and motifs of *Euplotes aediculatus,* and related sequences from *Schizosaccharomyces, Saccharomyces* sequences, and human telomerase. The polypeptides comprising telomeric subunits and functional polypeptides and ribonucleoproteins that contain these subunits are described as well. Cech *et al.,* International PCT Publication No. *WO 98/14592*, mentions in general terms the possibility of using antisense and ribozymes to down regulate the expression of human telomerase reverse transcriptase enzyme.

Summary Of The Invention

The invention features novel nucleic acid-based techniques [e.g., enzymatic nucleic acid molecules (ribozymes), antisense nucleic acids, 2-5A antisense chimeras, triplex DNA, antisense nucleic acids containing RNA cleaving chemical groups (Cook *et al.,* U.S. Patent 5,359,051)] and methods for their use to down regulate or inhibit the expression of telomerase enzyme.

In a preferred embodiment, the invention features use of one or more of the nucleic acid-based techniques to inhibit the expression of the genes encoding the protein subunits of the telomerase enzyme, preferably the catalytic subunit of the telomerase enzyme. Specifically, the invention features the use of nucleic acid-based techniques to specifically inhibit the expression of telomerase reverse transcriptase (TERT) gene.

In another preferred embodiment, the invention features the use of an enzymatic nucleic acid molecule, preferably in the hammerhead, NCH, G-cleaver and/or DNAzyme motif, to inhibit the expression TERT gene.

In another preferred embodiment, the invention features the inhibition or down regulation of telomerase activity by inhibiting or down regulating the expression of one or more activators of telomerase enzyme, such as protein encoded by *ras* gene. Such activator gene expression may be regulated by the use of nucleic acid-based techniques, such as enzymatic nucleic acid molecules and antisense oligonucleotides.

By "inhibit" it is meant that the activity of telomerase enzyme or level of RNAs or equivalent RNAs encoding one or more protein subunits of the telomerase enzyme is reduced below that observed in the absence of the nucleic acid. In one embodiment, inhibition with enzymatic nucleic acid molecule preferably is below that level observed in the presence of an enzymatically inactive or attenuated molecule that is able to bind to the same site on the target RNA, but is unable to cleave that RNA. In another embodiment, inhibition with antisense oligonucleotides is preferably below that level observed in the presence of for example, an oligonucleotide with scrambled sequence or with mismatches. In another embodiment, inhibition of TERT genes with the nucleic acid molecule of the instant invention is greater than in the presence of the nucleic acid molecule than in its absence. According to the invention, the activity of telomerase

enzyme or the level of RNA encoding one or more protein subunits of the telomerase enzyme is inhibited if it is at least 10% less, 20% less, 50% less, 75% less or even not active or present at all, in the presence of a nucleic acid of the invention relative to the level in the absence of such a nucleic acid.

As used herein, the term "telomerase activity" refers to enzyme activity that replicates, for example, the TTAGGG repeats at the ends of linear chromosomes. Telomerase activity is comprised by a ribonucleoprotein enzyme comprising one or more protein subunits and an RNA subunit. The enzymatic activity extends the 5'-recessed end of a linear chromosome using deoxyribonucleotides and an RNA sequence within the RNA subunit as a primer. Telomerase activity may be assayed as follows.

Samples to be assayed for telomerase activity are prepared by extraction into CHAPS lysis buffer (10mM Tris pH 7.5, 1mM $MgCl_2$, 1mM EGTA, 0.1 mM PMSF, 5mM -mercaptoethanol, 1mM DTT, 0.5% 3-[(3-cholamidopropyl)-dimethyl-amino]-1-propanesulfonate (CHAPS), 10% glycerol and 40 U/ml RNAse inhibitor (Promega, Madison, WI, U.S.A.). Cells are suspended in CHAPS lysis buffer and incubated on ice for 30 minutes, which allows lysis of 90-100% of cells. Lysate is then transferred to polyallomer centrifuge tubes and spun at 100,000 x g for 1 hour at 4 degrees C. The supernatant is the protein extract, and concentration ranges of 4-10 µg/µl are suitable for telomerase assay. Extracts may be concentrated if necessary using a Microcon Microfilter 30 (Amicron, Beverly, MA U.S.A.) according to the manufacturer's instructions. Extracts may be stored frozen at –80 degrees C until assayed.

Telomerase may be assayed according to Kim and Wu, *Nucl. Acids Res.* 25: 2595-2597, incorporated herein by reference. Briefly, for the telomerase assay, 2µg of protein extract is used. The extract is assayed in 50µl of reaction mixture containing 0.1 µg TS substrate primer (5'-AATCCGTCGAGCAGAGTT-3', end-labeled using alpha-^{32}P-ATP and T4 polynucleotide kinase), 0.1µg ACX return primer(5'-GCGCGG[CTTACC]$_3$ CTAACC-3'), 0.1 µg NT internal control primer (5'-ATCGCTTCTCGGCCTTTT-3'), 0.01 micromol TSNT internal control template (5'-AATCCGTCGAGCAGAGTTAAAAGGCCGAGAACGAT-3'), 50 µM each deoxynucleoside triphosphate, 2 U of Taq DNA polymerase, and 2 µl CHAPS protein extract, all in 1X TRAP buffer (20 mM Tris (pH 8.3), 68 mM KCl, 1.5 mM $MgCl_2$, 1 mM EGTA, 0.05% Tween 20). Each reaction is placed in a thermocycler block preheated to 30 C and incubated at 30 C for 10 minutes, then cycled for 27 cycles of 94 degrees C for 30 seconds, 60 degrees C for 30 seconds. Reaction products are separated

on a denaturing 8% polyacrylamide gel, followed by drying of the gel and autoradiography. The internal control (to control for possible Taq polymerase inhibition) generates a band of 36 nt. Comparison of radioactive signal integrated (*e.g.*, by phorphorimager analysis) for telomerase-extended bands with the radioactive signal from a reaction performed with a known amount of quantification standard template (termed R8; 5'-AATCCGTCGAGCAGAGTTAG $[GGTTAG]_7$-3') allows expression of telomerase activity as an absolute value. The absolute value = TPG (total product generated) =[(TP-TPí)/TI]/[(R8-B)/RI)] x 100, where TP = telomerase products from test extract, TPí = telomerase products from a heat-inactivated (75 C, 10 minutes) extract reaction, TI = the signal from the internal control, R8 = the signal from the R8 qualification standard template reaction, B = signal from a lysis buffer-only blank reaction, and RI = the internal control value for the reaction containing R8 template and NT and TSNT control primers. TPG values of 0-10,000 are possible, with the linear range being from approximately 1 to 1000 TPG. The range of 1 to 1000 TPG encompasses the minimum and maximum levels of telomerase activity in most tumor samples tested, while non-tumor cells most often have no telomerase activity (TPG approximately zero).

An alternative telomerase assay, which does not employ PCR amplification, is described by Raymond et al. 1999, *Br. J. Cancer* 80: 1332-1341.

By "enzymatic nucleic acid molecule" it is meant an RNA molecule which has complementarity in a substrate binding region to a specified gene target, and also has an enzymatic activity which is active to specifically cleave target RNA. That is, the enzymatic RNA molecule is able to intermolecularly cleave RNA and thereby inactivate a target RNA molecule. This complementary regions allow sufficient hybridization of the enzymatic RNA molecule to the target RNA and thus permit cleavage. One hundred percent complementarity between RNA and the target gene or target RNA is preferred, but complementarity as low as 50-75% may also be useful in this invention. The nucleic acids may be modified at the base, sugar, and/or phosphate groups. The term enzymatic nucleic acid is used interchangeably with phrases such as ribozymes, catalytic RNA, enzymatic RNA, catalytic DNA, aptazyme or aptamer-binding ribozyme, regulatable ribozyme, catalytic oligonucleotides, nucleozyme, DNAzyme, RNA enzyme, endoribonuclease, endonuclease, minizyme, leadzyme, oligozyme or DNA enzyme. All of these terminologies describe nucleic acid molecules with enzymatic activity. The specific enzymatic nucleic acid molecules described in the instant application are not

meant to be limiting and those skilled in the art will recognize that all that is important in an enzymatic nucleic acid molecule of this invention is that it have a specific substrate binding site which is complementary to one or more of the target nucleic acid regions, and that it have nucleotide sequences within or surrounding that substrate binding site which impart a nucleic acid cleaving activity to the molecule (Cech *et al.*, U.S. Patent No. 4,987,071; Cech *et al.,* 1988, JAMA).

By "enzymatic portion" or "catalytic domain" is meant that portion/region of the enzymatic nucleic acid molecule essential for cleavage of a nucleic acid substrate (for example see Figure 1).

By "substrate binding arm" or "substrate binding domain" is meant that portion/region of a ribozyme which is complementary to (*i.e.*, able to base-pair with) a portion of its substrate. Generally, such complementarity is 100%, but can be less if desired. For example, as few as 10 bases out of 14 may be base-paired. Such arms are shown generally in Figure 1. That is, these arms contain sequences within a ribozyme which are intended to bring ribozyme and target RNA together through complementary base-pairing interactions. The ribozyme of the invention may have binding arms that are contiguous or non-contiguous and may be of varying lengths. The length of the binding arm(s) are preferably greater than or equal to four nucleotides and of sufficient length to stably interact with the target RNA; specifically 12-100 nucleotides; more specifically 14-24 nucleotides long. If two binding arms are chosen, the design is such that the length of the binding arms are symmetrical (*i.e.,* each of the binding arms is of the same length; *e.g.,* five and five nucleotides, six and six nucleotides or seven and seven nucleotides long) or asymmetrical (*i.e.,* the binding arms are of different length; *e.g.,* six and three nucleotides; three and six nucleotides long; four and five nucleotides long; four and six nucleotides long; four and seven nucleotides long; and the like).

By DNAzyme is meant, an enzymatic nucleic acid molecule lacking a 2'-OH group. In particular embodiments the enzymatic nucleic acid molecule may have an attached linker(s) or other attached or associated groups, moieties, or chains containing one or more nucleotides with 2'-OH groups.

By "sufficient length" is meant an oligonucleotide of greater than or equal to 3 nucleotides, 5 nucleotides, 7 nucleotides, 9 nucleotides or even 12 nucleotides.

By "stably interact" is meant, interaction of the oligonucleotides with target nucleic acid (*e.g.,* by forming hydrogen bonds with complementary nucleotides in the target under physiological conditions).

By "equivalent" RNA to telomerase enzyme is meant to include those naturally occurring RNA molecules having homology (partial or complete) to nucleic acid sequences encoding telomerase proteins or encoding for proteins with similar function as telomerase in various organisms, including human, rodent, primate, rabbit, pig, protozoans, fungi, plants, and other microorganisms and parasites. The equivalent RNA sequence also includes in addition to the coding region, regions such as 5'-untranslated region, 3'-untranslated region, introns, intron-exon junction and the like.

By "homology" is meant the nucleotide sequence of two or more nucleic acid molecules is partially or completely identical.

By "antisense nucleic acid" it is meant a non-enzymatic nucleic acid molecule that binds to target RNA by means of RNA-RNA or RNA-DNA or RNA-PNA (protein nucleic acid; Egholm *et al.,* 1993 *Nature* 365, 566) interactions and alters the activity of the target RNA (for a review see Stein and Cheng, 1993 *Science* 261, 1004). Typically, antisense molecules will be complementary to a target sequence along a single contiguous sequence of the antisense molecule. However, in certain embodiments, an antisense molecule may bind to substrate such that the substrate molecule forms a loop, and/or an antisense molecule may bind such that the antisense molecule forms a loop. Thus, the antisense molecule may be complementary to two (or even more) non-contiguous substrate sequences or two (or even more) non-contiguous sequence portions of an antisense molecule may be complementary to a target sequence or both.

By "2-5A antisense chimera" it is meant, an antisense oligonucleotide containing a 5' phosphorylated 2'-5'-linked adenylate residues. These chimeras bind to target RNA in a sequence-specific manner and activate a cellular 2-5A-dependent ribonuclease which, in turn, cleaves the target RNA (Torrence *et al.,* 1993 *Proc. Natl. Acad. Sci. USA* 90, 1300).

By "triplex DNA" it is meant an oligonucleotide that can bind to a double-stranded DNA in a sequence-specific manner to form a triple-strand helix. Formation of such triple helix structure has been shown to inhibit transcription of the targeted gene (Duval-Valentin *et al.,* 1992 *Proc. Natl. Acad. Sci.USA* 89, 504).

By "gene" it is meant a nucleic acid that encodes an RNA.

By "complementarity" is meant that a nucleic acid can form hydrogen bond(s) with another RNA sequence by either traditional Watson-Crick or other non-traditional types. In reference to the nucleic molecules of the present invention, the binding free energy for a nucleic acid molecule with its target or complementary sequence is sufficient to allow the relevant function of the nucleic acid to proceed, e.g., ribozyme cleavage, antisense or triple helix inhibition. Determination of binding free energies for nucleic acid molecules is well known in the art (see, e.g., Turner et al., 1987, CSH Symp. Quant. Biol. LII pp.123-133; Frier et al., 1986, Proc. Nat. Acad. Sci. USA 83:9373-9377; Turner et al., 1987, J. Am. Chem. Soc. 109:3783-3785. A percent complementarity indicates the percentage of contiguous residues in a nucleic acid molecule which can form hydrogen bonds (e.g., Watson-Crick base pairing) with a second nucleic acid sequence (e.g., 5, 6, 7, 8, 9, 10 out of 10 being 50%, 60%, 70%, 80%, 90%, and 100% complementary). "Perfectly complementary" means that all the contiguous residues of a nucleic acid sequence will hydrogen bond with the same number of contiguous residues in a second nucleic acid sequence.

At least seven basic varieties of naturally-occurring enzymatic RNAs are known presently. Each can catalyze the hydrolysis of RNA phosphodiester bonds in *trans* (and thus can cleave other RNA molecules) under physiological conditions. Table I summarizes some of the characteristics of these ribozymes. In general, enzymatic nucleic acids act by first binding to a target RNA. Such binding occurs through the target binding portion of a enzymatic nucleic acid which is held in close proximity to an enzymatic portion of the molecule that acts to cleave the target RNA. Thus, the enzymatic nucleic acid first recognizes and then binds a target RNA through complementary base-pairing, and once bound to the correct site, acts enzymatically to cut the target RNA. Strategic cleavage of such a target RNA will destroy its ability to direct synthesis of an encoded protein. After an enzymatic nucleic acid has bound and cleaved its RNA target, it is released from that RNA to search for another target and can repeatedly bind and cleave new targets. Thus, a single ribozyme molecule is able to cleave many molecules of target RNA. In addition, the ribozyme is a highly specific inhibitor of gene expression, with the specificity of inhibition depending not only on the base-pairing mechanism of binding to the target RNA, but also on the mechanism of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a ribozyme.

The enzymatic nucleic acid molecule that cleave the specified sites in telomerase-specific RNAs represent a novel therapeutic approach to treat a variety of pathologic indications, including, cancer, tumorigenesis, restenosis and others.

In one of the preferred embodiments of the inventions described herein, the enzymatic nucleic acid molecule is formed in a hammerhead or hairpin motif, but may also be formed in the motif of a hepatitis delta virus, group I intron, group II intron or RNase P RNA (in association with an RNA guide sequence), *Neurospora* VS RNA, DNAzymes, NCH cleaving motifs, or G-cleavers. Examples of such hammerhead motifs are described by Dreyfus, *supra,* Rossi *et al.*, 1992, *AIDS Research and Human Retroviruses* 8, 183; of hairpin motifs by Hampel *et al.*, EP0360257, Hampel and Tritz, 1989 *Biochemistry* 28, 4929, Feldstein *et al.,* 1989, *Gene* 82, 53, Haseloff and Gerlach, 1989, *Gene*, 82, 43, and Hampel *et al.*, 1990 *Nucleic Acids Res.* 18, 299; Chowrira & McSwiggen, US. Patent No. 5,631,359; of the hepatitis delta virus motif is described by Perrotta and Been, 1992 *Biochemistry* 31, 16; of the RNase P motif by Guerrier-Takada *et al.*, 1983 *Cell* 35, 849; Forster and Altman, 1990, *Science* 249, 783; Li and Altman, 1996, *Nucleic Acids Res.* 24, 835; *Neurospora* VS RNA ribozyme motif is described by Collins (Saville and Collins, 1990 *Cell* 61, 685-696; Saville and Collins, 1991 *Proc. Natl. Acad. Sci. USA* 88, 8826-8830; Collins and Olive, 1993 *Biochemistry* 32, 2795-2799; Guo and Collins, 1995, *EMBO. J.* 14, 363); Group II introns are described by Griffin *et al.,* 1995, *Chem. Biol.* 2, 761; Michels and Pyle, 1995, *Biochemistry* 34, 2965; Pyle *et al.,* International PCT Publication No. *WO 96/22689*; of the Group I intron by Cech *et al.*, U.S. Patent 4,987,071 and of DNAzymes by Usman *et al.*, International PCT Publication No. WO 95/11304; Chartrand *et al.*, 1995, *NAR* 23, 4092; Breaker *et al.*, 1995, *Chem. Bio.* 2, 655; Santoro *et al.*, 1997, *PNAS* 94, 4262. NCH cleaving motifs are described in Ludwig & Sproat, International PCT Publication No. WO 98/58058; and G-cleavers are described in Kore *et al.*, 1998, *Nucleic Acids Research* 26, 4116-4120 and Eckstein *et al.,* International PCT Publication No. WO 99/16871. Additional motifs such as the Aptazyme (Breaker *et al.,* WO 98/43993), Amberzyme (Class I motif; Figure 3; Beigelman *et al.,* U.S. Serial No. 09/301,511) and Zinzyme (Beigelman *et al.,* U.S. Serial No. 09/301,511) can also be used in the present invention. These specific motifs are not limiting in the invention and those skilled in the art will

recognize that all that is important in an enzymatic nucleic acid molecule of this invention is that it has a specific substrate binding site which is complementary to one or more of the target gene RNA regions, and that it have nucleotide sequences within or surrounding that substrate binding site which impart an RNA cleaving activity to the molecule (Cech *et al.*, U.S. Patent No. 4,987,071).

In preferred embodiments of the present invention, a nucleic acid molecule, *e.g.*, an antisense molecule, a triplex DNA, or a ribozyme, is 13 to 100 nucleotides in length, *e.g.*, in specific embodiments 35, 36, 37, or 38 nucleotides in length (*e.g.*, for particular ribozymes or antisense). In particular embodiments, the nucleic acid molecule is 15-100, 17-100, 20-100, 21-100, 23-100, 25-100, 27-100, 30-100, 32-100, 35-100, 40-100, 50-100, 60-100, 70-100, or 80-100 nucleotides in length. Instead of 100 nucleotides being the upper limit on the length ranges specified above, the upper limit of the length range can be, for example, 30, 40, 50, 60, 70, or 80 nucleotides. Thus, for any of the length ranges, the length range for particular embodiments has lower limit as specified, with an upper limit as specified which is greater than the lower limit. For example, in a particular embodiment, the length range can be 35-50 nucleotides in length. All such ranges are expressly included. Also in particular embodiments, a nucleic acid molecule can have a length which is any of the lengths specified above, for example, 21 nucleotides in length.

In a preferred embodiment the invention provides a method for producing a class of nucleic acid –based gene inhibiting agents which exhibit a high degree of specificity for the RNA of a desired target. For example, the enzymatic nucleic acid molecule is preferably targeted to a highly conserved sequence region of target RNAs encoding telomerase proteins (specifically TERT gene) such that specific treatment of a disease or condition can be provided with either one or several nucleic acid molecules of the invention. Such nucleic acid molecules can be delivered exogenously to specific tissue or cellular targets as required. Alternatively, the nucleic acid molecules (*e.g.*, ribozymes and antisense) can be expressed from DNA and/or RNA vectors that are delivered to specific cells.

By "highly conserved sequence region" is meant a nucleotide sequence of one or more regions in a target gene does not vary significantly from one generation to the other or from one biological system to the other.

The nucleic acid-based inhibitors of telomerase expression are useful for the prevention of the diseases and conditions including cancer, macular degeneration, restenosis, certain infectious diseases, transplant rejection and autoimmune disease such as multiple sclerosis, lupus, and AIDS; Age related disease such as macular degeneration, skin ulceration, and rheumatoid arthritis. and any other diseases or conditions that are related to the levels of telomerase in a cell or tissue.

By "related" is meant that the reduction of telomerase expression (specifically TERT gene) RNA levels and thus reduction in the level of the respective protein will relieve, to some extent, the symptoms of the disease or condition.

The nucleic acid-based inhibitors of the invention are added directly, or can be complexed with cationic lipids, packaged within liposomes, or otherwise delivered to target cells or tissues. The nucleic acid or nucleic acid complexes can be locally administered to relevant tissues ex vivo, or in vivo through injection, infusion pump or stent, with or without their incorporation in biopolymers. In preferred embodiments, the enzymatic nucleic acid inhibitors comprise sequences which are complementary to the substrate sequences in **Tables III-VII**. Examples of such enzymatic nucleic acid molecules also are shown in **Tables III to VII**. Examples of such enzymatic nucleic acid molecules consist essentially of sequences defined in these Tables.

In yet another embodiment, the invention features antisense nucleic acid molecules and 2-5A chimera including sequences complementary to the substrate sequences shown in **tables III to VII**. Such nucleic acid molecules can include sequences as shown for the binding arms of the enzymatic nucleic acid molecules in **Tables III to VII**. Similarly, triplex molecules can be provided targeted to the corresponding DNA target regions, and containing the DNA equivalent of a target sequence or a sequence complementary to the specified target (substrate) sequence. Typically, antisense molecules will be complementary to a target sequence along a single contiguous sequence of the antisense molecule. However, in certain embodiments, an antisense molecule may bind to substrate such that the substrate molecule forms a loop, and/or an antisense molecule may bind such that the antisense molecule forms a loop. Thus, the antisense molecule may be complementary to two (or even more) non-contiguous substrate sequences or two (or even more) non-contiguous sequence portions of an antisense molecule may be complementary to a target sequence or both.

By "consists essentially of" is meant that the active ribozyme contains an enzymatic center or core equivalent to those in the examples, and binding arms able to bind mRNA such that cleavage at the target site occurs. Other sequences may be present which do not interfere with such cleavage. Thus, a core region may, for example, include one or more loop or stem-loop structures which do not prevent enzymatic activity. "X" in the sequences in Tables III and IV can be such a loop. A core sequence for a hammerhead ribozyme can be CUGAUGAG X CGAA where X=GCCGUUAGGC or other stem II region known in the art.

In another aspect of the invention, ribozymes or antisense molecules that cleave target RNA molecules and inhibit telomerase enzyme (specifically TERT) activity are expressed from transcription units inserted into DNA or RNA vectors. The recombinant vectors are preferably DNA plasmids or viral vectors. Ribozyme or antisense expressing viral vectors could be constructed based on, but not limited to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. Preferably, the recombinant vectors capable of expressing the ribozymes or antisense are delivered as described above, and persist in target cells. Alternatively, viral vectors may be used that provide for transient expression of ribozymes or antisense. Such vectors might be repeatedly administered as necessary. Once expressed, the ribozymes or antisense bind to the target RNA and inhibit its function or expression. Delivery of ribozyme or antisense expressing vectors could be systemic, such as by intravenous or intramuscular administration, by administration to target cells ex-planted from the patient followed by reintroduction into the patient, or by any other means that would allow for introduction into the desired target cell.

By "vectors" is meant any nucleic acid- and/or viral-based technique used to deliver a desired nucleic acid.

By "patient" is meant an organism which is a donor or recipient of explanted cells or the cells themselves. "Patient" also refers to an organism to which the nucleic acid molecules of the invention can be administered. Preferably, a patient is a mammal or mammalian cells. More preferably, a patient is a human or human cells.

The nucleic acid molecules of the instant invention, individually, or in combination or in conjunction with other drugs, can be used to treat diseases or conditions discussed above. For example, to treat a disease or condition associated with the levels of telomerase enzyme, the patient may be treated, or other appropriate cells

may be treated, as is evident to those skilled in the art, individually or in combination with one or more drugs under conditions suitable for the treatment.

In a further embodiment, the described molecules, such as antisense or ribozymes can be used in combination with other known treatments to treat conditions or diseases discussed above. For example, the described molecules could be used in combination with one or more known therapeutic agents to treat cancer.

In another preferred embodiment, the invention features nucleic acid-based inhibitors (*e.g.,* enzymatic nucleic acid molecules (ribozymes), antisense nucleic acids, 2-5A antisense chimeras, triplex DNA, antisense nucleic acids containing RNA cleaving chemical groups) and methods for their use to down regulate or inhibit the expression of genes (*e.g.,* TERT) capable of progression and/or maintenance of cancer.

In another preferred embodiment, the invention features nucleic acid-based techniques (*e.g.,* enzymatic nucleic acid molecules (ribozymes), antisense nucleic acids, 2-5A antisense chimeras, triplex DNA, antisense nucleic acids containing RNA cleaving chemical groups) and methods for their use to down regulate or inhibit the expression of TERT gene expression.

By "comprising" is meant including, but not limited to, whatever follows the word "comprising". Thus, use of the term "comprising" indicates that the listed elements are required or mandatory, but that other elements are optional and may or may not be present. By "consisting of" is meant including, and limited to, whatever follows the phrase "consisting of". Thus, the phrase "consisting of" indicates that the listed elements are required or mandatory, and that no other elements may be present. By "consisting essentially of" is meant including any elements listed after the phrase, and limited to other elements that do not interfere with or contribute to the activity or action specified in the disclosure for the listed elements. Thus, the phrase "consisting essentially of" indicates that the listed elements are required or mandatory, but that other elements are optional and may or may not be present depending upon whether or not they affect the activity or action of the listed elements.

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

Description Of The Preferred Embodiments

First the drawings will be described briefly.

Drawings

Figure 1 shows the secondary structure model for seven different classes of enzymatic nucleic acid molecules. Arrow indicates the site of cleavage. --------- indicate the target sequence. Lines interspersed with dots are meant to indicate tertiary interactions. - is meant to indicate base-paired interaction. **Group I Intron**: P1-P9.0 represent various stem-loop structures (Cech *et al.,* 1994, *Nature Struc. Bio.*, 1, 273). **RNase P (M1RNA)**: EGS represents external guide sequence (Forster *et al.,* 1990, *Science*, 249, 783; Pace *et al.,* 1990, *J. Biol. Chem.,* 265, 3587). **Group II Intron:** 5'SS means 5' splice site; 3'SS means 3'-splice site; IBS means intron binding site; EBS means exon binding site (Pyle *et al.,* 1994, *Biochemistry*, 33, 2716). **VS RNA:** I-VI are meant to indicate six stem-loop structures; shaded regions are meant to indicate tertiary interaction (Collins, International PCT Publication No. WO 96/19577). **HDV Ribozyme: :** I-IV are meant to indicate four stem-loop structures (Been *et al.,* US Patent No. 5,625,047). **Hammerhead Ribozyme: :** I-III are meant to indicate three stem-loop structures; stems I-III can be of any length and may be symmetrical or asymmetrical (Usman *et al.,* 1996, *Curr. Op. Struct. Bio.,* 1, 527). **Hairpin Ribozyme:** Helix 1, 4 and 5 can be of any length; Helix 2 is between 3 and 8 base-pairs long; Y is a pyrimidine; Helix 2 (H2) is provided with a least 4 base pairs (*i.e.,* n is 1, 2, 3 or 4) and helix 5 can be optionally provided of length 2 or more bases (preferably 3 - 20 bases, *i.e.,* m is from 1 - 20 or more). Helix 2 and helix 5 may be covalently linked by one or more bases (*i.e.,* r is ≥ 1 base). Helix 1, 4 or 5 may also be extended by 2 or more base pairs (*e.g.,* 4 - 20 base pairs) to stabilize the ribozyme structure, and preferably is a protein binding site. In each instance, each N and N' independently is any normal or modified base and each dash represents a potential base-pairing interaction. These nucleotides may be modified at the sugar, base or phosphate. Complete base-pairing is not required in the helices, but is preferred. Helix 1 and 4 can be of any size (*i.e.,* o and p is each independently from 0 to any number, *e.g.,* 20) as long as some base-pairing is maintained. Essential bases are shown as specific bases in the structure, but those in the art will recognize that one or more may be modified chemically (abasic, base, sugar and/or phosphate modifications) or replaced with another base without significant effect. Helix 4 can be formed from two separate molecules, *i.e.,* without a connecting loop. The connecting loop when present may be a ribonucleotide with or without modifications to its base, sugar or phosphate. "q" ≥ is 2 bases. The connecting loop

can also be replaced with a non-nucleotide linker molecule. H refers to bases A, U, or C. Y refers to pyrimidine bases. "_____" refers to a covalent bond. (Burke *et al.,* 1996, *Nucleic Acids & Mol. Biol.,* 10, 129; Chowrira *et al.,* US Patent No. 5,631,359).

Figure 2 shows examples of chemically stabilized ribozyme motifs. **HH Rz**, represents hammerhead ribozyme motif (Usman *et al.,* 1996, *Curr. Op. Struct. Bio.,* 1, 527); **NCH Rz** represents the NCH ribozyme motif (Ludwig & Sproat, International PCT Publication No. WO 98/58058); **G-Cleaver**, represents G-cleaver ribozyme motif (Kore *et al.*, 1998, *Nucleic Acids Research* 26, 4116-4120). **N** or **n**, represent independently a nucleotide which may be same or different and have complementarity to each other; **rI**, represents ribo-Inosine nucleotide; arrow indicates the site of cleavage within the target. Position 4 of the HH Rz and the NCH Rz is shown as having 2'-*C*-allyl moddification, but those skilled in the art will recognize that this position can be modified with other modifications well known in the art, so long as such modifications do not significantly inhibit the activity of the ribozyme.

Figure 3 shows an example of the Amberzyme ribozyme motif that is chemically stabilized (see for example Beigelman *et al.,* WO 99/55857; also referred to as Class I Motif).

Figure 4 shows an example of the Zinzyme A ribozyme motif that is chemically stabilized (see for example Beigelman *et al.,* WO 99/55857; also referred to as Class A Motif).

Mechanism of action of Nucleic Acid Molecules of the Invention

Antisense: Antisense molecules may be modified or unmodified RNA, DNA, or mixed polymer oligonucleotides and primarily function by specifically binding to matching sequences resulting in inhibition of peptide synthesis (Wu-Pong, Nov 1994, *BioPharm*, 20-33). The antisense oligonucleotide binds to target RNA by Watson Crick base-pairing and blocks gene expression by preventing ribosomal translation of the bound sequences either by steric blocking or by activating RNase H enzyme. Antisense molecules may also alter protein synthesis by interfering with RNA processing or transport from the nucleus into the cytoplasm (Mukhopadhyay & Roth, 1996, *Crit. Rev. in Oncogenesis* 7, 151-190).

In addition, binding of single stranded DNA to RNA may result in nuclease degradation of the heteroduplex (Wu-Pong, *supra*; Crooke, *supra*). To date, the only backbone modified DNA chemistry which will act as substrates for RNase H are phosphorothioates and phosphorodithioates. Recently it has been reported that 2'-arabino and 2'-fluoro arabino- containing oligos can also activate RNase H activity.

A number of antisense molecules have been described that utilize novel configurations of chemically modified nucleotides, secondary structure, and/or RNase H substrate domains (Woolf *et al.*, International PCT Publication No. WO 98/13526; Thompson *et al.*, USSN 60/082,404 which was filed on April 20, 1998; Hartmann *et al.*, USSN 60/101,174 which was filed on September 21, 1998) all of these are incorporated by reference herein in their entirety.

Triplex Forming Oligonucleotides (TFO): Single stranded DNA may be designed to bind to genomic DNA in a sequence specific manner. TFOs are comprised of pyrimidine-rich oligonucleotides which bind DNA helices through Hoogsteen Base-pairing (Wu-Pong, *supra*). The resulting triple helix composed of the DNA sense, DNA antisense, and TFO disrupts RNA synthesis by RNA polymerase. The TFO mechanism may result in gene expression or cell death since binding may be irreversible (Mukhopadhyay & Roth, *supra*)

2-5A Antisense Chimera: The 2-5A system is an interferon mediated mechanism for RNA degradation found in higher vertebrates (Mitra *et al.*, 1996, *Proc Nat Acad Sci USA* 93, 6780-6785). Two types of enzymes, 2-5A synthetase and RNase L, are required for RNA cleavage. The 2-5A synthetases require double stranded RNA to form 2'-5' oligoadenylates (2-5A). 2-5A then acts as an allosteric effector for utilizing RNase L which has the ability to cleave single stranded RNA. The ability to form 2-5A structures with double stranded RNA makes this system particularly useful for inhibition of viral replication.

(2'-5') oligoadenylate structures may be covalently linked to antisense molecules to form chimeric oligonucleotides capable of RNA cleavage (Torrence, *supra*). These molecules putatively bind and activate a 2-5A dependent RNase, the oligonucleotide/enzyme complex then binds to a target RNA molecule which can then be cleaved by the RNase enzyme.

Enzymatic Nucleic Acid: Seven basic varieties of naturally-occurring enzymatic RNAs are presently known. In addition, several *in vitro* selection (evolution) strategies (Orgel, 1979, *Proc. R. Soc. London,* B 205, 435) have been used to evolve new nucleic acid catalysts capable of catalyzing cleavage and ligation of phosphodiester linkages (Joyce, 1989, *Gene,* 82, 83-87; Beaudry *et al.,* 1992, *Science* 257, 635-641; Joyce, 1992, *Scientific American* 267, 90-97; Breaker *et al.,* 1994, *TIBTECH* 12, 268; Bartel *et al.,*1993, *Science* 261:1411-1418; Szostak, 1993, *TIBS* 17, 89-93; Kumar *et al.,* 1995, *FASEB J.,* 9, 1183; Breaker, 1996, *Curr. Op. Biotech.*, 7, 442; Santoro *et al.,* 1997, *Proc. Natl. Acad. Sci.,* 94, 4262; Tang *et al.,* 1997, *RNA* 3, 914; Nakamaye & Eckstein, 1994, *supra*; Long & Uhlenbeck, 1994, supra; Ishizaka et al., 1995, *supra*; Vaish *et al.,* 1997, *Biochemistry* 36, 6495; all of these are incorporated by reference herein). Each can catalyze a series of reactions including the hydrolysis of phosphodiester bonds in *trans* (and thus can cleave other RNA molecules) under physiological conditions.

Nucleic acid molecules of this invention will block to some extent telomerase protein expression (specifically TERT) and can be used to treat disease or diagnose disease associated with the levels of telomerase enzyme.

The enzymatic nature of a ribozyme has significant advantages, such as the concentration of ribozyme necessary to affect a therapeutic treatment is lower. This advantage reflects the ability of the ribozyme to act enzymatically. Thus, a single ribozyme molecule is able to cleave many molecules of target RNA. In addition, the ribozyme is a highly specific inhibitor, with the specificity of inhibition depending not only on the base-pairing mechanism of binding to the target RNA, but also on the mechanism of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can be chosen to completely eliminate catalytic activity of a ribozyme.

Nucleic acid molecules having an endonuclease enzymatic activity are able to repeatedly cleave other separate RNA molecules in a nucleotide base sequence-specific manner. Such enzymatic nucleic acid molecules can be targeted to virtually any RNA transcript, and achieved efficient cleavage *in vitro* (Zaug *et al.*, 324, *Nature* 429 1986 ; Uhlenbeck, 1987 *Nature* 328, 596; Kim et al., 84 *Proc. Natl. Acad. Sci. USA* 8788, 1987; Dreyfus, 1988, *Einstein Quart. J. Bio. Med.*, 6, 92; Haseloff and Gerlach, 334 *Nature* 585, 1988; Cech, 260 *JAMA* 3030, 1988; and Jefferies et al., 17 *Nucleic Acids Research* 1371, 1989; Santoro *et al.*, 1997 *supra*).

Because of their sequence specificity, *trans*-cleaving ribozymes show promise as therapeutic agents for human disease (Usman & McSwiggen, 1995 *Ann. Rep. Med. Chem.* **30**, 285-294; Christoffersen and Marr, 1995 *J. Med. Chem.* **38**, 2023-2037). Ribozymes can be designed to cleave specific RNA targets within the background of cellular RNA. Such a cleavage event renders the RNA non-functional and abrogates protein expression from that RNA. In this manner, synthesis of a protein associated with a disease state can be selectively inhibited.

Target sites

Targets for useful ribozymes and antisense nucleic acids can be determined as disclosed in Draper *et al.,* WO 93/23569; Sullivan *et al.,* WO 93/23057; Thompson *et al.,* WO 94/02595; Draper *et al.,* WO 95/04818; McSwiggen *et al.,* US Patent No. 5,525,468, and hereby incorporated by reference herein in totality. Other examples include the following PCT applications which concern inactivation of expression of disease-related genes: WO 95/23225, WO 95/13380, WO 94/02595, incorporated by reference herein. Rather than repeat the guidance provided in those documents here, below are provided specific examples of such methods, not limiting to those in the art. Ribozymes and antisense to such targets are designed as described in those applications and synthesized to be tested *in vitro* and *in vivo*, as also described. The sequence of human TERT RNAs were screened for optimal enzymatic nucleic acid and antisense target sites using a computer folding algorithm. Antisense, hammerhead, DNAzyme, NCH, or G-Cleaver ribozyme binding/cleavage sites were identified. These sites are shown in **Tables III to VII** (all sequences are 5' to 3' in the tables; X can be any base-paired sequence, the actual sequence is not relevant here). The nucleotide base position is noted in the Tables as that site to be cleaved by the designated type of enzymatic nucleic acid molecule. While human sequences can be screened and enzymatic nucleic acid molecule and/or antisense thereafter designed, as discussed in Stinchcomb *et al.,* WO 95/23225, mouse targeted ribozymes may be useful to test efficacy of action of the enzymatic nucleic acid molecule and/or antisense prior to testing in humans.

Antisense, hammerhead, DNAzyme, NCH, or G-Cleaver ribozyme binding/cleavage sites were identified. The nucleic acid molecules were individually analyzed by computer folding (Jaeger *et al.,* 1989 *Proc. Natl. Acad. Sci. USA*, 86, 7706) to assess whether the sequences fold into the appropriate secondary structure. Those nucleic acid molecules with unfavorable intramolecular interactions such as between the

binding arms and the catalytic core were eliminated from consideration. Varying binding arm lengths can be chosen to optimize activity.

Antisense, hammerhead, DNAzyme, NCH, or G-Cleaver ribozyme binding/cleavage sites were identified and were designed to anneal to various sites in the RNA target. The binding arms are complementary to the target site sequences described above. The nucleic acid molecules were chemically synthesized. The method of synthesis used follows the procedure for normal DNA/RNA synthesis as described below and in Usman *et al.,* 1987 *J. Am. Chem. Soc.*, 109, 7845; Scaringe *et al.,* 1990 *Nucleic Acids Res.*, 18, 5433; and Wincott *et al.,* 1995 *Nucleic Acids Res.* 23, 2677-2684; Caruthers *et al.*, 1992, *Methods in Enzymology* 211,3-19.

Synthesis of Nucleic acid Molecules

Synthesis of nucleic acids greater than 100 nucleotides in length is difficult using automated methods, and the therapeutic cost of such molecules is prohibitive. In this invention, small nucleic acid motifs ("small" refers to nucleic acid motifs no more than 100 nucleotides in length, preferably no more than 80 nucleotides in length, and most preferably no more than 50 nucleotides in length; *e.g.*, antisense oligonucleotides, hammerhead or the hairpin ribozymes) are preferably used for exogenous delivery. The simple structure of these molecules increases the ability of the nucleic acid to invade targeted regions of RNA structure. Exemplary molecules of the instant invention were chemically synthesized, and others can similarly be synthesized. Oligodeoxyribonucleotides were synthesized using standard protocols as described in Caruthers *et al.*, 1992, *Methods in Enzymology* 211,3-19, and is incorporated herein by reference.

The method of synthesis used for normal RNA including certain enzymatic nucleic acid molecules follows the procedure as described in Usman *et al.,* 1987 *J. Am. Chem. Soc.*, 109, 7845; Scaringe *et al.,* 1990 *Nucleic Acids Res.*, 18, 5433; and Wincott *et al.,* 1995 *Nucleic Acids Res.* 23, 2677-2684 Wincott *et al.,* 1997, *Methods Mol. Bio.*, 74, 59, and makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. In a non-limiting example, small scale syntheses were conducted on a 394 Applied Biosystems, Inc. synthesizer using a 0.2 μmol scale protocol with a 7.75 min coupling step for alkylsilyl protected nucleotides and a 2.5 min coupling step for 2'-O-methylated nucleotides. Table II outlines the amounts and the contact times of the reagents used in the synthesis

cycle. Alternatively, syntheses at the 0.2 μmol scale can be done on a 96-well plate synthesizer, such as the instrument produced by Protogene (Palo Alto, CA) with minimal modification to the cycle. A 15-fold excess (31 μL of 0.1 M = 3.1 μmol) of phosphoramidite and a 38.7-fold excess of S-ethyl tetrazole (31 μL of 0.25 M = 7.75 μmol) relative to polymer-bound 5'-hydroxyl was used in each coupling cycle. Average coupling yields on the 394 Applied Biosystems, Inc. synthesizer, determined by colorimetric quantitation of the trityl fractions, were 97.5-99%. Other oligonucleotide synthesis reagents for the 394 Applied Biosystems, Inc. synthesizer; detritylation solution was 3% TCA in methylene chloride (ABI); capping was performed with 16% *N*-methyl imidazole in THF (ABI) and 10% acetic anhydride/10% 2,6-lutidine in THF (ABI); oxidation solution was 16.9 mM I_2, 49 mM pyridine, 9% water in THF (PERSEPTIVE™). Burdick & Jackson Synthesis Grade acetonitrile was used directly from the reagent bottle. S-Ethyltetrazole solution (0.25 M in acetonitrile) was made up from the solid obtained from American International Chemical, Inc.

Deprotection of the RNA was performed using either a two-pot or one-pot protocol. For the two-pot protocol, the polymer-bound trityl-on oligoribonucleotide was transferred to a 4 mL glass screw top vial and suspended in a solution of 40% aq. methylamine (1 mL) at 65 °C for 10 min. After cooling to –20 °C, the supernatant was removed from the polymer support. The support was washed three times with 1.0 mL of EtOH:MeCN:H2O/3:1:1, vortexed and the supernatant was then added to the first supernatant. The combined supernatants, containing the oligoribonucleotide, were dried to a white powder. The base deprotected oligoribonucleotide was resuspended in anhydrous TEA/HF/NMP solution (300 μL of a solution of 1.5 mL N-methylpyrrolidinone, 750 μL TEA and 1 mL TEA•3HF to provide a 1.4 M HF concentration) and heated to 65 °C. After 1.5 h, the oligomer was quenched with 1.5 M NH_4HCO_3.

Alternatively, for the one-pot protocol, the polymer-bound trityl-on oligoribonucleotide was transferred to a 4 mL glass screw top vial and suspended in a solution of 33% ethanolic methylamine/DMSO:1/1 (0.8 mL) at 65 °C for 15 min. The vial was brought to r.t. TEA•3HF (0.1 mL) was added and the vial was heated at 65 °C for 15 min. The sample was cooled at –20 °C and then quenched with 1.5 M NH_4HCO_3.

For purification of the trityl-on oligomers, the quenched NH_4HCO_3 solution was loaded onto a C-18 containing cartridge that had been prewashed with acetonitrile followed by 50 mM TEAA. After washing the loaded cartridge with water, the RNA was detritylated with 0.5% TFA for 13 min. The cartridge was then washed again with water, salt exchanged with 1 M NaCl and washed with water again. The oligonucleotide was then eluted with 30% acetonitrile.

Inactive hammerhead ribozymes or binding attenuated control (BAC) oligonucleotides) were synthesized by substituting a U for G_5 and a U for A_{14} (numbering from Hertel, K. J., *et al.,* 1992, Nucleic Acids Res., 20, 3252). Similarly, one or more nucleotide substitutions can be introduced in other enzymatic nucleic acid molecules to inactivate the molecule and such molecules can serve as a negative control.

The average stepwise coupling yields were >98% (Wincott *et al.,* 1995 *Nucleic Acids Res.* 23, 2677-2684). Those of ordinary skill in the art will recognize that the scale of synthesis can be adapted to be larger or smaller than the example described above including but not limited to 96 well format, all that is important is the ratio of chemicals used in the reaction.

Alternatively, the nucleic acid molecules of the present invention can be synthesized separately and joined together post-synthetically, for example by ligation (Moore *et al.*, 1992, *Science* 256, 9923; Draper *et al.*, International PCT publication No. WO 93/23569; Shabarova *et al.*, 1991, *Nucleic Acids Research* 19, 4247; Bellon *et al.,* 1997, *Nucleosides & Nucleotides*, 16, 951; Bellon *et al.,* 1997 *Bioconjugate Chem.* 8, 204).

The nucleic acid molecules of the present invention are modified extensively to enhance stability by modification with nuclease resistant groups, for example, 2'-amino, 2'-*C*-allyl, 2'-flouro, 2'-*O*-methyl, 2'-H (for a review see Usman and Cedergren, 1992 *TIBS* 17, 34; Usman *et al.,* 1994 *Nucleic Acids Symp. Ser.* 31, 163). Ribozymes are purified by gel electrophoresis using general methods or are purified by high pressure liquid chromatography (HPLC; See Wincott *et al.,* Supra, the totality of which is hereby incorporated herein by reference) and are re-suspended in water.

The sequences of the ribozymes that are chemically synthesized, useful in this study, are shown in **Tables III to VII**. Those in the art will recognize that these sequences are representative only of many more such sequences where the enzymatic

portion of the ribozyme (all but the binding arms) is altered to affect activity. The ribozyme sequences listed in **Tables III to V and VII** may be formed of ribonucleotides or other nucleotides or non-nucleotides. Such ribozymes with enzymatic activity are equivalent to the ribozymes described specifically in the Tables.

Optimizing Activity of the nucleic acid molecule of the invention.

Chemically synthesizing synthesizing nucleic acid molecules with modifications (base, sugar and/or phosphate) that prevent their degradation by serum ribonucleases may increase their potency (see *e.g.,* Eckstein *et al.*, International Publication No. WO 92/07065; Perrault *et al.*, 1990 *Nature* 344, 565; Pieken et al., 1991 *Science* 253, 314; Usman and Cedergren, 1992 *Trends in Biochem. Sci.* 17, 334; Usman *et al.*, International Publication No. WO 93/15187; and Rossi *et al.*, International Publication No. WO 91/03162; Sproat, US Patent No. 5,334,711; and Burgin *et al., supra;* all of these describe various chemical modifications that can be made to the base, phosphate and/or sugar moieties of the nucleic acid molecules herein). Modifications which enhance their efficacy in cells, and removal of bases from nucleic acid molecules to shorten oligonucleotide synthesis times and reduce chemical requirements are desired. (All these publications are hereby incorporated by reference herein).

There are several examples in the art describing sugar, base and phosphate modifications that can be introduced into nucleic acid molecules with significant enhancement in their nuclease stability and efficacy. For example, oligonucleotides are modified to enhance stability and/or enhance biological activity by modification with nuclease resistant groups, for example, 2'-amino, 2'-*C*-allyl, 2'-flouro, 2'-*O*-methyl, 2'-H, nucleotide base modifications (for a review see Usman and Cedergren, 1992 *TIBS* 17, 34; Usman *et al.,* 1994 *Nucleic Acids Symp. Ser.* 31, 163; Burgin *et al.,* 1996 *Biochemistry* 35, 14090). Sugar modification of nucleic acid molecules have been extensively described in the art (see Eckstein *et al., International Publication* PCT No. WO 92/07065; Perrault *et al. Nature* 1990, *344*, 565-568; Pieken *et al. Science* 1991, *253*, 314-317; Usman and Cedergren, *Trends in Biochem. Sci.* 1992, *17*, 334-339; Usman *et al. International Publication* PCT No. WO 93/15187; Sproat, *US Patent* No. 5,334,711 and Beigelman *et al.,* 1995 *J. Biol. Chem.* 270, 25702; Beigelman *et al.,*

International PCT publication No. WO 97/26270; Beigelman *et al.,* US Patent No. 5,716,824; Usman *et al.,* US patent No. 5,627,053; Woolf *et al.*, International PCT Publication No. WO 98/13526; Thompson *et al.*, USSN 60/082,404 which was filed on April 20, 1998; Karpeisky *et al.,* 1998 *Tetrahedron Lett.* 39, 1131; ; all of the references are hereby incorporated in their totality by reference herein). Such publications describe general methods and strategies to determine the location of incorporation of sugar, base and/or phosphate modifications and the like into ribozymes without inhibiting catalysis, and are incorporated by reference herein. In view of such teachings, similar modifications can be used as described herein to modify the nucleic acid molecules of the instant invention.

While chemical modification of oligonucleotide internucleotide linkages with phosphorothioate, phosphorothioate, and/or 5'-methylphosphonate linkages improves stability, too many of these modifications may cause some toxicity. Therefore when designing nucleic acid molecules the amount of these internucleotide linkages should be minimized. The reduction in the concentration of these linkages should lower toxicity resulting in increased efficacy and higher specificity of these molecules.

Nucleic acid molecules having chemical modifications which maintain or enhance activity are provided. Such nucleic acid is also generally more resistant to nucleases than unmodified nucleic acid. Thus, in a cell and/or *in vivo* the activity may not be significantly lowered. Therapeutic nucleic acid molecules delivered exogenously must optimally be stable within cells until translation of the target RNA has been inhibited long enough to reduce the levels of the undesirable protein. This period of time varies between hours to days depending upon the disease state. Clearly, nucleic acid molecules must be resistant to nucleases in order to function as effective intracellular therapeutic agents. Improvements in the chemical synthesis of RNA and DNA (Wincott *et al.*, 1995 *Nucleic Acids Res.* 23, 2677; Caruthers *et al.*, 1992, *Methods in Enzymology* 211,3-19) incorporated by reference herein) have expanded the ability to modify nucleic acid molecules by introducing nucleotide modifications to enhance their nuclease stability as described above.

Use of these the nucleic acid-based molecules of the invention will lead to better treatment of the disease progression by affording the possibility of combination therapies (*e.g.,* multiple antisense or enzymatic nucleic acid molecules targeted to different genes, nucleic acid molecules coupled with known small molecule inhibitors, or intermittent treatment with combinations of molecules (including different motifs) and/or other chemical or biological molecules)). The treatment of patients with nucleic acid molecules may also include combinations of different types of nucleic acid molecules.

Therapeutic nucleic acid molecules (*e.g.,* enzymatic nucleic acid molecules and antisense nucleic acid molecules) delivered exogenously must optimally be stable within cells until translation of the target RNA has been inhibited long enough to reduce the levels of the undesirable protein. This period of time varies between hours to days depending upon the disease state. Clearly, these nucleic acid molecules must be resistant to nucleases in order to function as effective intracellular therapeutic agents. Improvements in the chemical synthesis of nucleic acid molecules described in the instant invention and in the art have expanded the ability to modify nucleic acid molecules by introducing nucleotide modifications to enhance their nuclease stability as described above.

By "enhanced enzymatic activity" is meant to include activity measured in cells and/or *in vivo* where the activity is a reflection of both catalytic activity and ribozyme stability. In this invention, the product of these properties is increased or not significantly (less that 10 fold) decreased *in vivo* compared to an all RNA ribozyme.

In yet another preferred embodiment, nucleic acid catalysts having chemical modifications which maintain or enhance enzymatic activity is provided. Such nucleic acid is also generally more resistant to nucleases than unmodified nucleic acid. Thus, in a cell and/or *in vivo* the activity may not be significantly lowered. As exemplified herein such ribozymes are useful in a cell and/or *in vivo* even if activity over all is reduced 10 fold (Burgin *et al.,* 1996, *Biochemistry*, 35, 14090). Such ribozymes herein are said to "maintain" the enzymatic activity on all RNA ribozyme.

In another aspect the nucleic acid molecules comprise a 5' and/or a 3'- cap structure.

By "cap structure" is meant chemical modifications, which have been incorporated at the terminus of the oligonucleotide (see for example Wincott *et al.,* WO 97/26270, incorporated by reference herein). These terminal modifications protect the nucleic acid molecule from exonuclease degradation, and may help in delivery and/or localization within a cell. The cap may be present at the 5'-terminus (5'-cap) or at the 3'-terminus (3'-cap) or may be present on both terminus. In non-limiting examples: the 5'-cap is selected from the group comprising inverted abasic residue (moiety), 4',5'-methylene nucleotide; 1-(beta-D-erythrofuranosyl) nucleotide, 4'-thio nucleotide, carbocyclic nucleotide; 1,5-anhydrohexitol nucleotide; L-nucleotides; alpha-nucleotides; modified base nucleotide; phosphorodithioate linkage; *threo*-pentofuranosyl nucleotide; acyclic 3',4'-seco nucleotide; acyclic 3,4-dihydroxybutyl nucleotide; acyclic 3,5-dihydroxypentyl nucleotide, 3'-3'-inverted nucleotide moiety; 3'-3'-inverted abasic moiety; 3'-2'-inverted nucleotide moiety; 3'-2'-inverted abasic moiety; 1,4-butanediol phosphate; 3'-phosphoramidate; hexylphosphate; aminohexyl phosphate; 3'-phosphate; 3'-phosphorothioate; phosphorodithioate; or bridging or non-bridging methylphosphonate moiety (for more details see Beigelman *et al.,* International PCT publication No. WO 97/26270, incorporated by reference herein). In yet another preferred embodiment the 3'-cap is selected from a group comprising, 4',5'-methylene nucleotide; 1-(beta-D-erythrofuranosyl) nucleotide; 4'-thio nucleotide, carbocyclic nucleotide; 5'-amino-alkyl phosphate; 1,3-diamino-2-propyl phosphate, 3-aminopropyl phosphate; 6-aminohexyl phosphate; 1,2-aminododecyl phosphate; hydroxypropyl phosphate; 1,5-anhydrohexitol nucleotide; L-nucleotide; alpha-nucleotide; modified base nucleotide; phosphorodithioate; *threo*-pentofuranosyl nucleotide; acyclic 3',4'-seco nucleotide; 3,4-dihydroxybutyl nucleotide; 3,5-dihydroxypentyl nucleotide, 5'-5'-inverted nucleotide moeity; 5'-5'-inverted abasic moiety; 5'-phosphoramidate; 5'-phosphorothioate; 1,4-butanediol phosphate; 5'-amino; bridging and/or non-bridging 5'-phosphoramidate, phosphorothioate and/or phosphorodithioate, bridging or non bridging methylphosphonate and 5'-mercapto moieties (for more details see Beaucage and Iyer, 1993, *Tetrahedron* 49, 1925; incorporated by reference herein). By the term "non-nucleotide" is meant any group or compound which can be incorporated into a nucleic acid chain in the place of one or more nucleotide units, including either sugar and/or phosphate substitutions, and allows the remaining bases to exhibit their enzymatic activity. The group or compound is abasic in that it does not contain a commonly recognized nucleotide base, such as adenosine, guanine, cytosine, uracil or thymine.

An "alkyl" group refers to a saturated aliphatic hydrocarbon, including straight-chain, branched-chain, and cyclic alkyl groups. Preferably, the alkyl group has 1 to 12 carbons. More preferably it is a lower alkyl of from 1 to 7 carbons, more preferably 1 to 4 carbons. The alkyl group may be substituted or unsubstituted. When substituted the substituted group(s) is preferably, hydroxyl, cyano, alkoxy, =O, =S, NO_2 or $N(CH_3)_2$, amino, or SH. The term also includes alkenyl groups which are unsaturated hydrocarbon groups containing at least one carbon-carbon double bond, including straight-chain, branched-chain, and cyclic groups. Preferably, the alkenyl group has 1 to 12 carbons. More preferably it is a lower alkenyl of from 1 to 7 carbons, more preferably 1 to 4 carbons. The alkenyl group may be substituted or unsubstituted. When substituted the substituted group(s) is preferably, hydroxyl, cyano, alkoxy, =O, =S, NO_2, halogen, $N(CH_3)_2$, amino, or SH. The term "alkyl" also includes alkynyl groups which have an unsaturated hydrocarbon group containing at least one carbon-carbon triple bond, including straight-chain, branched-chain, and cyclic groups. Preferably, the alkynyl group has 1 to 12 carbons. More preferably it is a lower alkynyl of from 1 to 7 carbons, more preferably 1 to 4 carbons. The alkynyl group may be substituted or unsubstituted. When substituted the substituted group(s) is preferably, hydroxyl, cyano, alkoxy, =O, =S, NO_2 or $N(CH_3)_2$, amino or SH.

Such alkyl groups may also include aryl, alkylaryl, carbocyclic aryl, heterocyclic aryl, amide and ester groups. An "aryl" group refers to an aromatic group which has at least one ring having a conjugated p electron system and includes carbocyclic aryl, heterocyclic aryl and biaryl groups, all of which may be optionally substituted. The preferred substituent(s) of aryl groups are halogen, trihalomethyl, hydroxyl, SH, OH, cyano, alkoxy, alkyl, alkenyl, alkynyl, and amino groups. An "alkylaryl" group refers to an alkyl group (as described above) covalently joined to an aryl group (as described above. Carbocyclic aryl groups are groups wherein the ring atoms on the aromatic ring are all carbon atoms. The carbon atoms are optionally substituted. Heterocyclic aryl groups are groups having from 1 to 3 heteroatoms as ring atoms in the aromatic ring and the remainder of the ring atoms are carbon atoms. Suitable heteroatoms include oxygen, sulfur, and nitrogen, and include furanyl, thienyl, pyridyl, pyrrolyl, N-lower alkyl pyrrolo, pyrimidyl, pyrazinyl, imidazolyl and the like, all optionally substituted. An

"amide" refers to an -C(O)-NH-R, where R is either alkyl, aryl, alkylaryl or hydrogen. An "ester" refers to an -C(O)-OR', where R is either alkyl, aryl, alkylaryl or hydrogen.

By "nucleotide" as used herein is as recognized in the art to include natural bases (standard), and modified bases well known in the art. Such bases are generally located at the 1' position of a nucleotide sugar moiety. Nucleotides generally comprise a base, sugar and a phosphate group. The nucleotides can be unmodified or modified at the sugar, phosphate and/or base moiety, (also referred to interchangeably as nucleotide analogs, modified nucleotides, non-natural nucleotides, non-standard nucleotides and other; see for example, Usman and McSwiggen, *supra*; Eckstein *et al.,* International PCT Publication No. WO 92/07065; Usman *et al.,* International PCT Publication No. WO 93/15187; Uhlman & Peyman, *supra*) all are hereby incorporated by reference herein). There are several examples of modified nucleic acid bases known in the art and has recently been summarized by Limbach *et al.,* 1994, *Nucleic Acids Res.* 22, 2183. Some of the non-limiting examples of base modifications that can be introduced into nucleic acid molecules include, inosine, purine, pyridin-4-one, pyridin-2-one, phenyl, pseudouracil, 2, 4, 6-trimethoxy benzene, 3-methyl uracil, dihydrouridine, naphthyl, aminophenyl, 5-alkylcytidines (*e.g.*, 5-methylcytidine), 5-alkyluridines (*e.g.*, ribothymidine), 5-halouridine (*e.g.*, 5-bromouridine) or 6-azapyrimidines or 6-alkylpyrimidines (*e.g.* 6-methyluridine), propyne, and others (Burgin *et al.,* 1996, *Biochemistry*, 35, 14090; Uhlman & Peyman, *supra*). By "modified bases" in this aspect is meant nucleotide bases other than adenine, guanine, cytosine and uracil at 1' position or their equivalents; such bases may be used at any position, for example, within the catalytic core of an enzymatic nucleic acid molecule and/or in the substrate-binding regions of the nucleic acid molecule.

By "abasic" is meant sugar moieties lacking a base or having other chemical groups in place of a base at the 1' position.

By “ribonucleotide” is meant a nucleotide with one of the bases adenine, cytosine, guanine, or uracil joined to the 1' carbon of -D-ribo-furanose.

By "unmodified nucleoside" is meant one of the bases adenine, cytosine, guanine, uracil joined to the 1' carbon of β-D-ribo-furanose.

By "modified nucleoside" is meant any nucleotide base which contains a modification in the chemical structure of an unmodified nucleotide base, sugar and/or phosphate.

In connection with 2'-modified nucleotides as described for the present invention, by "amino" is meant 2'-NH_2 or 2'-*O*- NH_2, which may be modified or unmodified. Such modified groups are described, for example, in Eckstein et al., U.S. Patent 5,672,695 and Matulic-Adamic et al., WO 98/28317, respectively, which are both incorporated by reference in their entireties.

Various modifications to nucleic acid (*e.g.,* antisense and ribozyme) structure can be made to enhance the utility of these molecules. Such modifications will enhance shelf-life, half-life *in vitro,* stability, and ease of introduction of such oligonucleotides to the target site, *e.g.,* to enhance penetration of cellular membranes, and confer the ability to recognize and bind to targeted cells.

Use of these molecules will lead to better treatment of the disease progression by affording the possibility of combination therapies (e.g., multiple ribozymes targeted to different genes, ribozymes coupled with known small molecule inhibitors, or intermittent treatment with combinations of ribozymes (including different ribozyme motifs) and/or other chemical or biological molecules). The treatment of patients with nucleic acid molecules may also include combinations of different types of nucleic acid molecules. Therapies may be devised which include a mixture of ribozymes (including different ribozyme motifs), antisense and/or 2-5A chimera molecules to one or more targets to alleviate symptoms of a disease.

Administration of Nucleic Acid Molecules

Methods for the delivery of nucleic acid molecules are described in Akhtar *et al.,* 1992, *Trends Cell Bio.*, 2, 139; and *Delivery Strategies for Antisense Oligonucleotide Therapeutics*, ed. Akhtar, 1995 which are both incorporated herein by reference. Sullivan *et al.*, PCT WO 94/02595, further describes the general methods for delivery of enzymatic RNA molecules. These protocols may be utilized for the delivery of virtually any nucleic acid molecule. Nucleic acid molecules may be administered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels,

cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. For some indications, nucleic acid molecules may be directly delivered *ex vivo* to cells or tissues with or without the aforementioned vehicles. Alternatively, the nucleic acid/vehicle combination is locally delivered by direct injection or by use of a catheter, infusion pump or stent. Other routes of delivery include, but are not limited to, intravascular, intramuscular, subcutaneous or joint injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions of nucleic acid delivery and administration are provided in Sullivan *et al.*, supra and Draper *et al.*, PCT WO93/23569 which have been incorporated by reference herein.

The molecules of the instant invention can be used as pharmaceutical agents. Pharmaceutical agents prevent, inhibit the occurrence, or treat (alleviate a symptom to some extent, preferably all of the symptoms) of a disease state in a patient.

The negatively charged polynucleotides of the invention can be administered (*e.g.*, RNA, DNA or protein) and introduced into a patient by any standard means, with or without stabilizers, buffers, and the like, to form a pharmaceutical composition. When it is desired to use a liposome delivery mechanism, standard protocols for formation of liposomes can be followed. The compositions of the present invention may also be formulated and used as tablets, capsules or elixirs for oral administration; suppositories for rectal administration; sterile solutions; suspensions for injectable administration; and the like.

The present invention also includes pharmaceutically acceptable formulations of the compounds described. These formulations include salts of the above compounds, *e.g.*, acid addition salts, for example, salts of hydrochloric, hydrobromic, acetic acid, and benzene sulfonic acid.

A pharmacological composition or formulation refers to a composition or formulation in a form suitable for administration, *e.g.*, systemic administration, into a cell or patient, preferably a human. Suitable forms, in part, depend upon the use or the route of entry, for example oral, transdermal, or by injection. Such forms should not prevent the composition or formulation to reach a target cell (*i.e.*, a cell to which the

negatively charged polymer is desired to be delivered to). For example, pharmacological compositions injected into the blood stream should be soluble. Other factors are known in the art, and include considerations such as toxicity and forms which prevent the composition or formulation from exerting its effect.

By "systemic administration" is meant *in vivo* systemic absorption or accumulation of drugs in the blood stream followed by distribution throughout the entire body. Administration routes which lead to systemic absorption include, without limitations: intravenous, subcutaneous, intraperitoneal, inhalation, oral, intrapulmonary and intramuscular. Each of these administration routes expose the desired negatively charged polymers, *e.g.,* nucleic acids, to an accessible diseased tissue. The rate of entry of a drug into the circulation has been shown to be a function of molecular weight or size. The use of a liposome or other drug carrier comprising the compounds of the instant invention can potentially localize the drug, for example, in certain tissue types, such as the tissues of the reticular endothelial system (RES). A liposome formulation which can facilitate the association of drug with the surface of cells, such as, lymphocytes and macrophages is also useful. This approach may provide enhanced delivery of the drug to target cells by taking advantage of the specificity of macrophage and lymphocyte immune recognition of abnormal cells, such as the cancer cells.

The invention also features the use of the composition comprising surface-modified liposomes containing poly (ethylene glycol) lipids (PEG-modified, or long-circulating liposomes or stealth liposomes). These formulations offer an method for increasing the accumulation of drugs in target tissues. This class of drug carriers resists opsonization and elimination by the mononuclear phagocytic system (MPS or RES), thereby enabling longer blood circulation times and enhanced tissue exposure for the encapsulated drug (Lasic *et al. Chem. Rev.* 1995, **95**, 2601-2627; Ishiwata *et al.*, *Chem. Pharm. Bull.* 1995, **43**, 1005-1011). Such liposomes have been shown to accumulate selectively in tumors, presumably by extravasation and capture in the neovascularized target tissues (Lasic *et al., Science* 1995, **267**, 1275-1276; Oku *et al.,*1995, *Biochim. Biophys. Acta*, **1238**, 86-90). The long-circulating liposomes enhance the pharmacokinetics and pharmacodynamics of DNA and RNA, particularly compared to

conventional cationic liposomes which are known to accumulate in tissues of the MPS (Liu *et al.*, *J. Biol. Chem.* 1995, **42**, 24864-24870; Choi *et al.,* International PCT Publication No. WO 96/10391; Ansell *et al.,* International PCT Publication No. WO 96/10390; Holland *et al.,* International PCT Publication No. WO 96/10392; all of these are incorporated by reference herein). Long-circulating liposomes are also likely to protect drugs from nuclease degradation to a greater extent compared to cationic liposomes, based on their ability to avoid accumulation in metabolically aggressive MPS tissues such as the liver and spleen. All of these references are incorporated by reference herein.

The present invention also includes compositions prepared for storage or administration which include a pharmaceutically effective amount of the desired compounds in a pharmaceutically acceptable carrier or diluent. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described, for example, in *Remington's Pharmaceutical Sciences*, Mack Publishing Co. (A.R. Gennaro edit. 1985) hereby incorporated by reference herein. For example, preservatives, stabilizers, dyes and flavoring agents may be provided. These include sodium benzoate, sorbic acid and esters of *p*-hydroxybenzoic acid. In addition, antioxidants and suspending agents may be used.

A pharmaceutically effective dose is that dose required to prevent, inhibit the occurrence, or treat (alleviate a symptom to some extent, preferably all of the symptoms) of a disease state. The pharmaceutically effective dose depends on the type of disease, the composition used, the route of administration, the type of mammal being treated, the physical characteristics of the specific mammal under consideration, concurrent medication, and other factors which those skilled in the medical arts will recognize. Generally, an amount between 0.1 mg/kg and 100 mg/kg body weight/day of active ingredients is administered dependent upon potency of the negatively charged polymer.

The nucleic acid molecules of the present invention may also be administered to a patient in combination with other therapeutic compounds to increase the overall

therapeutic effect. The use of multiple compounds to treat an indication may increase the beneficial effects while reducing the presence of side effects.

Alternatively, certain of the nucleic acid molecules of the instant invention can be expressed within cells from eukaryotic promoters (*e.g.,* Izant and Weintraub, 1985 *Science* 229, 345; McGarry and Lindquist, 1986 *Proc. Natl. Acad. Sci.* USA 83, 399; Scanlon *et al.,* 1991, *Proc. Natl. Acad. Sci. USA*, 88, 10591-5; Kashani-Sabet *et al.,* 1992 *Antisense Res. Dev.,* 2, 3-15; Dropulic *et al.,* 1992 *J. Virol,* 66, 1432-41; Weerasinghe *et al.,* 1991 *J. Virol,* **65**, 5531-4; Ojwang *et al.,* 1992 *Proc. Natl. Acad. Sci. USA* 89, 10802-6; Chen *et al.,* 1992 *Nucleic Acids Res.,* 20, 4581-9; Sarver *et al.,* 1990 *Science* 247, 1222-1225; Thompson *et al.,* 1995 *Nucleic Acids Res.* 23, 2259; Good *et al.,* 1997, *Gene* Therapy, 4, 45; all of the references are hereby incorporated in their totality by reference herein). Those skilled in the art realize that any nucleic acid can be expressed in eukaryotic cells from the appropriate DNA/RNA vector. The activity of such nucleic acids can be augmented by their release from the primary transcript by a ribozyme (Draper *et al.,* PCT WO 93/23569, and Sullivan *et al.,* PCT WO 94/02595; Ohkawa *et al.,* 1992 *Nucleic Acids Symp. Ser.,* 27, 15-6; Taira *et al.,* 1991, *Nucleic Acids Res.,* 19, 5125-30; Ventura *et al.,* 1993 *Nucleic Acids Res.,* 21, 3249-55; Chowrira *et al.,* 1994 *J. Biol. Chem.* 269, 25856; all of the references are hereby incorporated in their totality by reference herein).

In another aspect of the invention, RNA molecules of the present invention are preferably expressed from transcription units (see for example Couture *et al.,* 1996, *TIG.,* 12, 510) inserted into DNA or RNA vectors. The recombinant vectors are preferably DNA plasmids or viral vectors. Ribozyme expressing viral vectors could be constructed based on, but not limited to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. Preferably, the recombinant vectors capable of expressing the nucleic acid molecules are delivered as described above, and persist in target cells. Alternatively, viral vectors may be used that provide for transient expression of nucleic acid molecules. Such vectors might be repeatedly administered as necessary. Once expressed, the nucleic acid molecule binds to the target mRNA. Delivery of nucleic acid molecule expressing vectors could be systemic, such as by intravenous or intra-

muscular administration, by administration to target cells ex-planted from the patient followed by reintroduction into the patient, or by any other means that would allow for introduction into the desired target cell (for a review see Couture *et al.,* 1996, *TIG.,* 12, 510).

In one aspect the invention features, an expression vector comprising nucleic acid sequence encoding at least one of the nucleic acid molecules of the instant invention is disclosed. The nucleic acid sequence encoding the nucleic acid molecule of the instant invention is operable linked in a manner which allows expression of that nucleic acid molecule.

In another aspect the invention features, the expression vector comprises: a transcription initiation region (*e.g.,* eukaryotic pol I, II or III initiation region); b) a transcription termination region (*e.g.,* eukaryotic pol I, II or III termination region); c) a gene encoding at least one of the nucleic acid catalyst of the instant invention; and wherein said gene is operably linked to said initiation region and said termination region, in a manner which allows expression and/or delivery of said nucleic acid molecule. The vector may optionally include an open reading frame (ORF) for a protein operably linked on the 5' side or the 3'-side of the gene encoding the nucleic acid catalyst of the invention; and/or an intron (intervening sequences).

Transcription of the nucleic acid molecule sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters will be expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type will depend on the nature of the gene regulatory sequences (enhancers, silencers, etc.) present nearby. Prokaryotic RNA polymerase promoters are also used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells (Elroy-Stein and Moss, 1990 *Proc. Natl. Acad. Sci. U S A*, 87, 6743-7; Gao and Huang 1993 *Nucleic Acids Res.*, 21, 2867-72; Lieber et al., 1993 *Methods Enzymol.,* 217, 47-66; Zhou et al., 1990 *Mol. Cell. Biol.*, 10, 4529-37). Several investigators have demonstrated that nucleic acid molecules, such as ribozymes expressed from such

promoters can function in mammalian cells (e.g. Kashani-Sabet et al., 1992 *Antisense Res. Dev.,* 2, 3-15; Ojwang et al., 1992 *Proc. Natl. Acad. Sci. U S A*, 89, 10802-6; Chen *et al.*, 1992 *Nucleic Acids Res.*, 20, 4581-9; Yu et al., 1993 *Proc. Natl. Acad. Sci. U S A*, 90, 6340-4; L'Huillier *et al.*, 1992 *EMBO J.* 11, 4411-8; Lisziewicz *et al.*, 1993 *Proc. Natl. Acad. Sci. U. S. A.*, 90, 8000-4; Thompson *et al.,* 1995 *Nucleic Acids Res.* 23, 2259; Sullenger & Cech, 1993, *Science,* 262, 1566). More specifically, transcription units such as the ones derived from genes encoding U6 small nuclear (snRNA), transfer RNA (tRNA) and adenovirus VA RNA are useful in generating high concentrations of desired RNA molecules such as ribozymes in cells (Thompson *et al., supra*; Couture and Stinchcomb, *1996, supra*; Noonberg *et al.,* 1994, *Nucleic Acid Res.*, 22, 2830; Noonberg *et al.,* US Patent No. 5,624,803; Good *et al.,* 1997, *Gene Ther.* 4, 45; Beigelman *et al.,* International PCT Publication No. *WO 96/18736*; all of these publications are incorporated by reference herein. The above ribozyme transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated virus vectors), or viral RNA vectors (such as retroviral or alphavirus vectors) (for a review see Couture and Stinchcomb, *1996, supra).*

In yet another aspect the invention features an expression vector comprising nucleic acid sequence encoding at least one of the nucleic acid molecules of the invention, in a manner which allows expression of that nucleic acid molecule. The expression vector comprises in one embodiment; a) a transcription initiation region; b) a transcription termination region; c) a gene encoding at least one said nucleic acid molecule; and wherein said gene is operably linked to said initiation region and said termination region, in a manner which allows expression and/or delivery of said nucleic acid molecule. In another preferred embodiment the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an open reading frame; d) a gene encoding at least one said nucleic acid molecule, wherein said gene is operably linked to the 3'-end of said open reading frame; and wherein said gene is operably linked to said initiation region, said open reading frame and said termination region, in a manner which allows expression and/or delivery of said nucleic acid molecule. In yet another embodiment the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an intron; d) a

gene encoding at least one said nucleic acid molecule; and wherein said gene is operably linked to said initiation region, said intron and said termination region, in a manner which allows expression and/or delivery of said nucleic acid molecule. In another embodiment, the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an intron; d) an open reading frame; e) a gene encoding at least one said nucleic acid molecule, wherein said gene is operably linked to the 3'-end of said open reading frame; and wherein said gene is operably linked to said initiation region, said intron, said open reading frame and said termination region, in a manner which allows expression and/or delivery of said nucleic acid molecule.

Examples.

The following are non-limiting examples showing the selection, isolation, synthesis and activity of nucleic acids of the instant invention.

The following examples demonstrate the selection and design of Antisense, hammerhead, DNAzyme, NCH, or G-Cleaver ribozyme molecules and binding/cleavage sites within TERT RNA.

Example 1: Identification of Potential Target Sites in Human TERT RNA

The sequence of human TERT was screened for accessible sites using a computer folding algorithm. Regions of the RNA that did not form secondary folding structures and contained potential ribozyme and/or antisense binding/cleavage sites were identified. The sequences of these cleavage sites are shown in **tables III-VII.**

Example 2: Selection of Enzymatic Nucleic Acid Cleavage Sites in Human TERT RNA

To test whether the sites predicted by the computer-based RNA folding algorithm corresponded to accessible sites in TERT RNA, 10 hammerhead ribozyme and three G-Cleaver ribozyme sites were selected for further analysis (Table VI). Ribozyme target sites were chosen by analyzing sequences of Human TERT (Nakamura *et al.*, 1997 Science 277, 955-959; Genbank sequence accession number: NM_003219) and prioritizing the sites on the basis of folding. Ribozymes were designed that could bind each target and were individually analyzed by computer folding (Christoffersen *et al.*,

1994 *J. Mol. Struc. Theochem,* 311, 273; Jaeger *et al.*, 1989, *Proc. Natl. Acad. Sci. USA*, **86**, 7706) to assess whether the ribozyme sequences fold into the appropriate secondary structure. Those ribozymes with unfavorable intramolecular interactions between the binding arms and the catalytic core were eliminated from consideration. As noted below, varying binding arm lengths can be chosen to optimize activity. Generally, at least 5 bases on each arm are able to bind to, or otherwise interact with, the target RNA.

Example 3: Chemical Synthesis and Purification of Ribozymes for Efficient Cleavage of TERT RNA

Ribozymes were designed to anneal to various sites in the RNA message. The binding arms are complementary to the target site sequences described above. The ribozymes were chemically synthesized. The method of synthesis used followed the procedure for normal RNA synthesis as described above and in Usman et al., (1987 J. Am. Chem. Soc., 109, 7845), Scaringe et al., (1990 Nucleic Acids Res., 18, 5433) and Wincott et al., supra, and made use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. The average stepwise coupling yields were >98%.

Ribozymes were also synthesized from DNA templates using bacteriophage T7 RNA polymerase (Milligan and Uhlenbeck, 1989, Methods Enzymol. 180, 51). Ribozymes were purified by gel electrophoresis using general methods or were purified by high pressure liquid chromatography (HPLC; See Wincott et al., supra; the totality of which is hereby incorporated herein by reference) and were resuspended in water. The sequences of the chemically synthesized ribozymes used in this study are shown below in **Table III-VII.**

Example 4: Ribozyme Cleavage of TERT RNA Target *in vitro*

Ribozymes targeted to the human TERT RNA are designed and synthesized as described above. These ribozymes can be tested for cleavage activity *in vitro*, for example using the following procedure. The target sequences and the nucleotide location within the TERT RNA are given in Tables III-VII.

Cleavage Reactions: Full-length or partially full-length, internally-labeled target RNA for ribozyme cleavage assay is prepared by *in vitro* transcription in the presence of [a-^{32}P] CTP, passed over a G 50 Sephadex column by spin chromatography and used as

substrate RNA without further purification. Alternately, substrates are 5'-^{32}P-end labeled using T4 polynucleotide kinase enzyme. Assays are performed by pre-warming 15 μl of a 2X concentration of purified ribozyme in ribozyme cleavage buffer (50 mM Tris-HCl, pH 7.5 at 37°C, 10 mM $MgCl_2$) and the cleavage reaction was initiated by adding the 2X ribozyme mix to an equal volume (15 μl) of substrate RNA (maximum of 1-5 nM; 5×10^5 to 1×10^7 cpm) that was also pre-warmed in cleavage buffer. As an initial screen, assays are carried out for 1 hour at 37°C using a final concentration of either 40 nM or 1 mM ribozyme, *i.e.,* ribozyme excess. The reaction is quenched by the addition of an equal volume (30 μl) of 95% formamide, 20 mM EDTA, 0.05% bromophenol blue and 0.05% xylene cyanol after which the sample is heated to 95°C for 2 minutes, quick chilled and loaded onto a denaturing polyacrylamide gel. Substrate RNA and the specific RNA cleavage products generated by ribozyme cleavage are visualized on an autoradiograph of the gel. The percentage of cleavage is determined by Phosphor Imager® quantitation of bands representing the intact substrate and the cleavage products.

Cell Culture Models

Various methods have been developed to assay telomerase activity *in vitro*. The most widely used method to characterize telomerase activity is the telomeric repeat amplification protocol (TRAP). TRAP utilizes RT-PCR of cellular extracts to measure telomerase activity by making the amount of PCR target dependant upon the biochemical activity of the enzyme (Kim, N. W., 1997, Nucleic Acids Research, 25, 2595-2597).

Human cell culture studies have been established to assay inhibition of telomerase activity in human carcinomas responding to various therapeutics. A human breast cancer model for studying telomerase inhibitors is described (Raymond, E., 1999, Br. J. Cancer, 80, 1332-1341). Human studies of telomerase expression as related to various other cancers are described including cervical cancer (Nakano, K., 1998, Am. J. Pathol, 153, 857-864), endometrial cancer (Kyo, S., 1999, Int. J. Cancer, 80, 60-63), meningeal carcinoma (Kleinschmidt-DeMasters, B. K., 1998, J. Neurol. Sci., 161, 124-134), lung carcinoma (Yashima, K., 1997, Cancer Reseach, 57, 2372-2377), testicular cancer in response to cisplatin (Burger, A. M., 1997, Eur. J. Cancer, 33, 638-644), and ovarian carcinoma (Counter, C. M., 1994, Proc. Natl. Acad. Sci., 91, 2900-2904).

Animal Models

A variety of animal models have been designed to assay telomerase activity *in vivo*. Inhibition of telomerase activity has been analyzed in rats via cell proliferation studies with MNU (N-methyl-N-nitosurea) induced mammary carcinomas in response to treatment with 4-(hydroxyphenyl)retinamide (4-HPR), a known inhibitor of mammary carcinogenesis in animal models and premenopausal women (Bednarek, A., 1999, Carcinogenesis, 20, 879-883). The method of Bednarek et al. uses N-methyl-N-nitrosourea (MNU)-induced mammary carcinomas in rats to analyze the effect of telomerase inhibitors *in vivo*. MNU-induced tumors express high telomerase activity. Female virgin Sprague-Dawley rats are injected twice with MNU (50 mg/kg body weight) at days 43 and 50 days of age. Mammary tumors are allowed to grow to 4-8 mm before commencing treatment with an agent, such as 4-(hydroxyphenyl) retinamide (used by Bednarek *et al.*) or a nucleic acid of the invention being tested as a modulator of telomerase activity. Following treatment with an agent for 0 to 6 weeks, telomerase activity is assayed using the TRAP method on CHAPS-extracted tumor-cell protein samples. A decrease of 10% or more in telomerase activity relative to the level in tumors of untreated animals indicates an agent is a telomerase inhibitor. Additional studies have focused on the up-regulation of telomerase in transformed cell lines from animal and human model systems (Zhang, P. B., 1998, Leuk. Res., 22, 509-516), (Chadeneau, C., 1995, Oncogene, 11, 893-898), (Greenberg, R., 1999, Oncogene, 18, 1219-1226).

Indications

Particular degenerative and disease states that can be associated with telomerase expression modulation include but are not limited to:

- Cancer: Almost all human tumors have detectable telomerase activity (Shay, J. W., 1997, Eur. J. Cancer, 33, 787-791). Treatment with telomerase inhibitors may provide effective cancer therapy with minimal side effects in normal somatic cells that lack telomerase activity. The therapeutic potential exists for the treatment of a wide variety of cancer types.

- Restinosis: Telomerase inhibition in vascular smooth muscle cells may inhibit restinosis by limiting proliferation of these cells.

- Infectious disease: Telomerase inhibition in infectious cell types that express telomerase activity may provide selective antibiotic activity. Such treatment may prove especially effective in protozoan-based infection such as Giardia and Leishmaniasis.

- Transplant rejection: Telomerase inhibition in endothelial cell types may demonstrate selective immunnosuppressant activity. Activation of telomerase in transplant cells could benefit grafting success through increased proliferative potential.

- Autoimmune disease: Telomerase modulation in various immune cells may prove beneficial in treating diseases such as multiple sclerosis, lupus, and AIDS.

- Age related disease: Activation of telomerase expression in cells at or nearing senescence as a result of advanced age or premature aging could benefit conditions such as macular degeneration, skin ulceration, and rheumatoid arthritis.

The present body of knowledge in telomerase research indicates the need for methods to assay telomerase activity and for compounds that can regulate telomerase expression for research, diagnostic, and therapeutic use.

Gemcytabine and cyclophosphamide are non-limiting examples of chemotherapeutic agents that can be combined with or used in conjunction with the nucleic acid molecules (*e.g.* ribozymes and antisense molecules) of the instant invention. Those skilled in the art will recognize that other drugs such as anti-cancer compounds and therapies can be similarly be readily combined with the nucleic acid molecules of the instant invention (*e.g.* ribozymes and antisense molecules) and are hence within the scope of the instant invention. Such compounds and therapies are well known in the art (see for example *Cancer: Principles and Practice of Oncology*, Volumes 1 and 2, eds Devita, V.T., Hellman, S., and Rosenberg, S.A., J.B. Lippincott Company, Philadelphia, USA; incorporated herein by reference) and include, without limitations, antifolates; fluoropyrimidines; cytarabine; purine analogs; adenosine analogs; amsacrine; topoisomerase I inhibitors; anthrapyrazoles; retinoids; antibiotics such as bleomycin, anthacyclins, mitomycin C, dactinomycin, and mithramycin; hexamethylmelamine; dacarbazine; l-asperginase; platinum analogs; alkylating agents such as nitrogen mustard, melphalan, chlorambucil, busulfan, ifosfamide, 4-hydroperoxycyclophosphamide, nitrosoureas, thiotepa; plant derived compounds such as

vinca alkaloids, epipodophyllotoxins, taxol; Tomaxifen; radiation therapy; surgery; nutritional supplements; gene therapy; radiotherapy such as 3D-CRT; immunotoxin therapy such as ricin, monoclonal antibodies herceptin; and the like. For combination therapy, the nucleic acids of the invention are prepared in one of two ways. First, the agents are physically combined in a preparation of nucleic acid and chemotherapeutic agent, such as a mixture of a nucleic acid of the invention encapsulated in liposomes and ifosfamide in a solution for intravenous administration, wherein both agents are present in a therapeutically effective concentration (e.g., ifosfamide in solution to deliver 1000-1250 mg/m2/day and liposome-associated nucleic acid of the invention in the same solution to deliver 0.1-100 mg/kg/day). Alternatively, the agents are administered separately but simultaneously in their respective effective doses (e.g., 1000-1250 mg/m2/d ifosfamide and 0.1 to 100 mg/kg/day nucleic acid of the invention).

Diagnostic uses

The nucleic acid molecules of this invention (*e.g., ribozymes)* may be used as diagnostic tools to examine genetic drift and mutations within diseased cells or to detect the presence of TERT RNA in a cell. The close relationship between ribozyme activity and the structure of the target RNA allows the detection of mutations in any region of the molecule which alters the base-pairing and three-dimensional structure of the target RNA. By using multiple ribozymes described in this invention, one may map nucleotide changes which are important to RNA structure and function *in vitro*, as well as in cells and tissues. Cleavage of target RNAs with ribozymes may be used to inhibit gene expression and define the role (essentially) of specified gene products in the progression of disease. In this manner, other genetic targets may be defined as important mediators of the disease. These experiments will lead to better treatment of the disease progression by affording the possibility of combinational therapies (*e.g.,* multiple ribozymes targeted to different genes, ribozymes coupled with known small molecule inhibitors, or intermittent treatment with combinations of ribozymes and/or other chemical or biological molecules). Other *in vitro* uses of ribozymes of this invention are well known in the art, and include detection of the presence of mRNAs associated with TERT-related condition. Such RNA is detected by determining the presence of a cleavage product after treatment with a ribozyme using standard methodology.

In a specific example, ribozymes which can cleave only wild-type or mutant forms of the target RNA are used for the assay. The first ribozyme is used to identify wild-type RNA present in the sample and the second ribozyme will be used to identify mutant RNA in the sample. As reaction controls, synthetic substrates of both wild-type and mutant RNA will be cleaved by both ribozymes to demonstrate the relative ribozyme efficiencies in the reactions and the absence of cleavage of the "non-targeted" RNA species. The cleavage products from the synthetic substrates will also serve to generate size markers for the analysis of wild-type and mutant RNAs in the sample population. Thus each analysis will require two ribozymes, two substrates and one unknown sample which will be combined into six reactions. The presence of cleavage products will be determined using an RNAse protection assay so that full-length and cleavage fragments of each RNA can be analyzed in one lane of a polyacrylamide gel. For example, the cleavage reactions are performed in ribozyme cleavage buffer with a final reaction volume of 30 µl per reaction as follows: 1) ribozyme specific for (*i.e.,* that specifically cleaves) wild-type RNA (*wt* ribozyme; 40 nM final reaction concentration) is incubated with wild type substrate (1-5 nM final reaction concentration) at 37°C for one hour; 2) wt ribozyme is incubated with mutant substrate (same conditions); 3) wt ribozyme (40 nM final concentration) is incubated with 50 µg of total RNA from the individual being tested, at 37°C for one hour; 4) same as (1), only with 40 nM final concentration of ribozyme specific for mutant RNA; 5) same as (2), only with ribozyme specific for mutant RNA; and 6) same as (3), only with ribozyme specific for mutant RNA. Cleavage products are precipitated with ethanol and resuspended in 20 µl of hybridization buffer for RNAse protection with 5 x 10^5 to 1 x 10^7 cpm of ^{32}P-labeled RNA probe. Hybridization buffer consists of the following (per reaction): 24µl Formamide, 2µl 0.6M PIPES, 2.4µl 5M NaCl , 0.3µl 0.1M EDTA, and DEPC-treated water to 30 µl. Samples are heated at 95°C for 10 minutes, then incubated 4 hours at 55°C (hybridization temperatures may be estimated by one of skill in the art and optimized empirically for a given probe:target combination without undue experimentation). Following hybridization, hybridized sequences are digested with ribonucleases by the addition of 350 µl of RNase digestion buffer (300 mM NaOAc, 10 mM Tris, 5 mM EDTA) followed by addition of 1 µl of 4mg/ml RNase A and 0.4 µl of 10u/µl RNase T1. Digestion is carried out for 45 minutes to 1 hour at 30°C, followed by the addition of 10 µl of 20% SDS and 2.5 µl of 10mg/ml Proteinase K. Samples are incubated at 37°C for 15-20 minutes followed by phenol/chloroform/isoamyl alcohol (25:24:1) extraction and precipitation with ethanol. Samples are resuspended in

formamide loading buffer, heat denatured and electrophoresed on a denaturing polyacrylamide gel. Protected cleavage products are visualized by autoradiography and quantitated by phosphorimager analysis. It is not absolutely required to quantify the results to gain insight into the expression of mutant RNAs and putative risk of the desired phenotypic changes in target cells. The expression of mRNA whose protein product is implicated in the development of the phenotype (*i.e.*, TERT) is adequate to establish risk. If probes of comparable specific activity are used for both transcripts, then a qualitative comparison of RNA levels will be adequate and will decrease the cost of the initial diagnosis. Higher mutant form to wild-type ratios will be correlated with higher risk whether RNA levels are compared qualitatively or quantitatively.

Additional Uses

Potential usefulness of sequence-specific enzymatic nucleic acid molecules of the instant invention might have many of the same applications for the study of RNA that DNA restriction endonucleases have for the study of DNA (Nathans *et al.*, 1975 *Ann. Rev. Biochem.* 44:273). For example, the pattern of restriction fragments could be used to establish sequence relationships between two related RNAs, and large RNAs could be specifically cleaved to fragments of a size more useful for study. The ability to engineer sequence specificity of the enzymatic nucleic acid molecule is ideal for cleavage of RNAs of unknown sequence. Applicant describes the use of nucleic acid molecules to down-regulate gene expression of target genes in bacterial, microbial, fungal, viral, and eukaryotic systems including plant, or mammalian cells.

All patents and publications mentioned in the specification are indicative of the levels of skill of those skilled in the art to which the invention pertains. All references cited in this disclosure are incorporated by reference to the same extent as if each reference had been incorporated by reference in its entirety individually.

One skilled in the art would readily appreciate that the present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent therein. The methods and compositions described herein as presently representative of preferred embodiments are exemplary and are not intended as limitations on the scope of the invention. Changes therein and other uses will occur to

those skilled in the art, which are encompassed within the spirit of the invention, are defined by the scope of the claims.

It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention. Thus, such additional embodiments are within the scope of the present invention and the following claims.

The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising", "consisting essentially of" and "consisting of" may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments, optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the description and the appended claims.

In addition, where features or aspects of the invention are described in terms of Markush groups or other grouping of alternatives, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group or other group.

Other embodiments are within the following claims.

TABLE I

Characteristics of naturally occurring ribozymes

Group I Introns

- Size: ~150 to >1000 nucleotides.
- Requires a U in the target sequence immediately 5' of the cleavage site.
- Binds 4-6 nucleotides at the 5'-side of the cleavage site.
- Reaction mechanism: attack by the 3'-OH of guanosine to generate cleavage products with 3'-OH and 5'-guanosine.
- Additional protein cofactors required in some cases to help folding and maintainance of the active structure.
- Over 300 known members of this class. Found as an intervening sequence in *Tetrahymena thermophila* rRNA, fungal mitochondria, chloroplasts, phage T4, blue-green algae, and others.
- Major structural features largely established through phylogenetic comparisons, mutagenesis, and biochemical studies [i,ii].
- Complete kinetic framework established for one ribozyme [iii,iv,v,vi].
- Studies of ribozyme folding and substrate docking underway [vii,viii,ix].
- Chemical modification investigation of important residues well established [x,xi].
- The small (4-6 nt) binding site may make this ribozyme too non-specific for targeted RNA cleavage, however, the Tetrahymena group I intron has been used to repair a "defective" β-galactosidase message by the ligation of new β-galactosidase sequences onto the defective message [xii].

RNAse P RNA (M1 RNA)

- Size: ~290 to 400 nucleotides.
- RNA portion of a ubiquitous ribonucleoprotein enzyme.
- Cleaves tRNA precursors to form mature tRNA [xiii].
- Reaction mechanism: possible attack by M^{2+}-OH to generate cleavage products with 3'-OH and 5'-phosphate.
- RNAse P is found throughout the prokaryotes and eukaryotes. The RNA subunit has been sequenced from bacteria, yeast, rodents, and primates.
- Recruitment of endogenous RNAse P for therapeutic applications is possible through hybridization of an External Guide Sequence (EGS) to the target RNA [xiv,xv]
- Important phosphate and 2' OH contacts recently identified [xvi,xvii]

Group II Introns

- Size: >1000 nucleotides.
- Trans cleavage of target RNAs recently demonstrated [xviii,xix].
- Sequence requirements not fully determined.
- Reaction mechanism: 2'-OH of an internal adenosine generates cleavage products with 3'-OH and a "lariat" RNA containing a 3'-5' and a 2'-5' branch point.

- Only natural ribozyme with demonstrated participation in DNA cleavage [xx,xxi] in addition to RNA cleavage and ligation.
- Major structural features largely established through phylogenetic comparisons [xxii].
- Important 2' OH contacts beginning to be identified [xxiii]
- Kinetic framework under development [xxiv]

Neurospora VS RNA

- Size: ~144 nucleotides.
- Trans cleavage of hairpin target RNAs recently demonstrated [xxv].
- Sequence requirements not fully determined.
- Reaction mechanism: attack by 2'-OH 5' to the scissile bond to generate cleavage products with 2',3'-cyclic phosphate and 5'-OH ends.
- Binding sites and structural requirements not fully determined.
- Only 1 known member of this class. Found in Neurospora VS RNA.

Hammerhead Ribozyme

(see text for references)

- Size: ~13 to 40 nucleotides.
- Requires the target sequence UH immediately 5' of the cleavage site.
- Binds a variable number nucleotides on both sides of the cleavage site.
- Reaction mechanism: attack by 2'-OH 5' to the scissile bond to generate cleavage products with 2',3'-cyclic phosphate and 5'-OH ends.
- 14 known members of this class. Found in a number of plant pathogens (virusoids) that use RNA as the infectious agent.
- Essential structural features largely defined, including 2 crystal structures [xxvi,xxvii]
- Minimal ligation activity demonstrated (for engineering through *in vitro* selection) [xxviii]
- Complete kinetic framework established for two or more ribozymes [xxix].
- Chemical modification investigation of important residues well established [xxx].

Hairpin Ribozyme

- Size: ~50 nucleotides.
- Requires the target sequence GUC immediately 3' of the cleavage site.
- Binds 4-6 nucleotides at the 5'-side of the cleavage site and a variable number to the 3'-side of the cleavage site.
- Reaction mechanism: attack by 2'-OH 5' to the scissile bond to generate cleavage products with 2',3'-cyclic phosphate and 5'-OH ends.
- 3 known members of this class. Found in three plant pathogen (satellite RNAs of the tobacco ringspot virus, arabis mosaic virus and chicory yellow mottle virus) which uses RNA as the infectious agent.
- Essential structural features largely defined [xxxi,xxxii,xxxiii,xxxiv]
- Ligation activity (in addition to cleavage activity) makes ribozyme amenable to engineering through *in vitro* selection [xxxv]
- Complete kinetic framework established for one ribozyme [xxxvi].
- Chemical modification investigation of important residues begun [xxxvii,xxxviii].

Hepatitis Delta Virus (HDV) Ribozyme

- Size: ~60 nucleotides.
- Trans cleavage of target RNAs demonstrated [xxxix].
- Binding sites and structural requirements not fully determined, although no sequences 5' of cleavage site are required. Folded ribozyme contains a pseudoknot structure [xl].
- Reaction mechanism: attack by 2'-OH 5' to the scissile bond to generate cleavage products with 2',3'-cyclic phosphate and 5'-OH ends.
- Only 2 known members of this class. Found in human HDV.
- Circular form of HDV is active and shows increased nuclease stability [xli]

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Table II: 0.2 µmol RNA Synthesis Cycle

Reagents	Equivalents	Amounts (microL)	Wait time (sec)
Phosphoramidites	15	31	465
SET	38.7	31	465
Acetic anhydride	655	124	5
N-methyl-imidazole	1245	124	5
TCA	700	732	10
Iodine	20.6	244	15

* Wait time does not include contact time during delivery.

Table III: Human telomerase reverse transcriptase (TERT) Hammerhead Ribozyme and Target Sequence

nt. Position	Ribozyme Sequence	Seq ID Nos.	Substrate Sequence	Seq ID Nos.
13	CGCAGCAG CUGAUGAG X CGAA ACGCAGCG		CGCTGCGT C CTGCTGCG	
68	GCAGCGGG CUGAUGAG X CGAA AGCGCGCG		CGCGCGCT C CCCGCTGC	
90	GCAGCAGG CUGAUGAG X CGAA AGCGCACG		CGTGCGCT C CCTGCTGC	
108	CCUCGCGG CUGAUGAG X CGAA AGUGGCUG		CAGCCACT A CCGCGAGG	
135	GCCGCACG CUGAUGAG X CGAA ACGUGGCC		GGCCACGT T CGTGCGGC	
136	CGCCGCAC CUGAUGAG X CGAA AACGUGGC		GCCACGTT C GTGCGGCG	
194	CGCGCGGA CUGAUGAG X CGAA AGCCGCCG		CGGCGGCT T TCCGCGCG	
195	GCGCGCGG CUGAUGAG X CGAA AAGCCGCC		GGCGGCTT T CCGCGCGC	
196	AGCGCGCG CUGAUGAG X CGAA AAAGCCGC		GCGGCTTT C CGCGCGCT	
264	GGCGGAAG CUGAUGAG X CGAA AGGGGGCG		CGCCCCCT C CTTCCGCC	
267	CCUGGCGG CUGAUGAG X CGAA AGGAGGGG		CCCCTCCT T CCGCCAGG	
268	ACCUGGCG CUGAUGAG X CGAA AAGGAGGG		CCCTCCTT C CGCCAGGT	
279	UCAGGCAG CUGAUGAG X CGAA ACACCUGG		CCAGGTGT C CTGCCTGA	
351	CGAAGCCG CUGAUGAG X CGAA AGGCCAGC		GCTGGCCT T CGGCTTCG	
352	GCGAAGCC CUGAUGAG X CGAA AAGGCCAG		CTGGCCTT C GGCTTCGC	
357	GCAGCGCG CUGAUGAG X CGAA AGCCGAAG		CTTCGGCT T CGCGCTGC	
358	AGCAGCGC CUGAUGAG X CGAA AAGCCGAA		TTCGGCTT C GCGCTGCT	
399	UGGUGGUG CUGAUGAG X CGAA AGGCCUCG		CGAGGCCT T CACCACCA	
400	CUGGUGGU CUGAUGAG X CGAA AAGGCCUC		GAGGCCTT C ACCACCAG	
420	UGGGCAGG CUGAUGAG X CGAA AGCUGCGC		GCGCAGCT A CCTGCCCA	
505	AGCAGGUG CUGAUGAG X CGAA ACCAGCAC		GTGCTGGT T CACCTGCT	
506	CAGCAGGU CUGAUGAG X CGAA AACCAGCA		TGCTGGTT C ACCTGCTG	
529	AGCACAAA CUGAUGAG X CGAA AGCGCGCA		TGCGCGCT C TTTGTGCT	
531	CCAGCACA CUGAUGAG X CGAA AGAGCGCG		CGCGCTCT T TGTGCTGG	
532	ACCAGCAC CUGAUGAG X CGAA AAGAGCGC		GCGCTCTT T GTGCTGGT	
545	GCAGCUGG CUGAUGAG X CGAA AGCCACCA		TGGTGGCT C CCAGCTGC	
558	ACACCUGG CUGAUGAG X CGAA AGGCGCAG		CTGCGCCT A CCAGGTGT	
582	CGAGCUGG CUGAUGAG X CGAA ACAGCGGC		GCCGCTGT A CCAGCTCG	
589	GCAGCGCC CUGAUGAG X CGAA AGCUGGUA		TACCAGCT C GGCGCTGC	
602	CCGGGCCU CUGAUGAG X CGAA AGUGGCAG		CTGCCACT C AGGCCCGG	
626	GGGUCCAC CUGAUGAG X CGAA AGCGUGUG		CACACGCT A GTGGACCC	
644	GCAUCCCA CUGAUGAG X CGAA ACGCCUUC		GAAGGCGT C TGGGATGC	
671	CCUGACGC CUGAUGAG X CGAA AUGGUUCC		GGAACCAT A GCGTCAGG	
676	GCCUCCCU CUGAUGAG X CGAA ACGCUAUG		CATAGCGT C AGGGAGGC	
691	CCCAGGGG CUGAUGAG X CGAA ACCCCGGC		GCCGGGGT C CCCCTGGG	
749	CAACGGCA CUGAUGAG X CGAA ACUUCGGC		GCCGAAGT C TGCCGTTG	
756	UCUUGGGC CUGAUGAG X CGAA ACGGCAGA		TCTGCCGT T GCCCAAGA	
808	CCCUGCCC CUGAUGAG X CGAA ACGGGCGU		ACGCCCGT T GGGCAGGG	
819	GGGCCCAG CUGAUGAG X CGAA ACCCCUGC		GCAGGGGT C CTGGGCCC	
863	CACACAGA CUGAUGAG X CGAA ACCACGGU		ACCGTGGT T TCTGTGTG	
864	CCACACAG CUGAUGAG X CGAA AACCACGG		CCGTGGTT T CTGTGTGG	
865	ACCACACA CUGAUGAG X CGAA AAACCACG		CGTGGTTT C TGTGTGGT	
876	UGGCAGGU CUGAUGAG X CGAA ACACCACA		TGTGGTGT C ACCTGCCA	

Table III

906	CCUCCAAA CUGAUGAG X CGAA AGGUGGCU		AGCCACCT C TTTGGAGG	
908	ACCCUCCA CUGAUGAG X CGAA AGAGGUGG		CCACCTCT T TGGAGGGT	
909	CACCCUCC CUGAUGAG X CGAA AAGAGGUG		CACCTCTT T GGAGGGTG	
922	GUGCCAGA CUGAUGAG X CGAA AGCGCACC		GGTGCGCT C TCTGGCAC	
924	GCGUGCCA CUGAUGAG X CGAA AGAGCGCA		TGCGCTCT C TGGCACGC	
939	AUGGGUGG CUGAUGAG X CGAA AGUGGCGC		GCGCCACT C CCACCCAT	
948	GGCCCACG CUGAUGAG X CGAA AUGGGUGG		CCACCCAT C CGTGGGCC	
981	GCGAUGUG CUGAUGAG X CGAA AUGGGGGG		CCCCCCAT C CACATCGC	
987	GUGGCCGC CUGAUGAG X CGAA AUGUGGAU		ATCCACAT C GCGGCCAC	
1001	GUCCCAGG CUGAUGAG X CGAA ACGUGGUG		CACCACGT C CCTGGGAC	
1016	CGGGGGAC CUGAUGAG X CGAA AGGCGUGU		ACACGCCT T GTCCCCCG	
1019	CACCGGGG CUGAUGAG X CGAA ACAAGGCG		CGCCTTGT C CCCCGGTG	
1029	UCUCGGCG CUGAUGAG X CGAA ACACCGGG		CCCGGTGT A CGCCGAGA	
1047	AGUAGAGG CUGAUGAG X CGAA AGUGCUUG		CAAGCACT T CCTCTACT	
1048	GAGUAGAG CUGAUGAG X CGAA AAGUGCUU		AAGCACTT C CTCTACTC	
1051	GAGGAGUA CUGAUGAG X CGAA AGGAAGUG		CACTTCCT C TACTCCTC	
1053	CUGAGGAG CUGAUGAG X CGAA AGAGGAAG		CTTCCTCT A CTCCTCAG	
1056	CGCCUGAG CUGAUGAG X CGAA AGUAGAGG		CCTCTACT C CTCAGGCG	
1059	UGUCGCCU CUGAUGAG X CGAA AGGAGUAG		CTACTCCT C AGGCGACA	
1086	GUAGGAAG CUGAUGAG X CGAA AGGGCCGC		GCGGCCCT C CTTCCTAC	
1089	UGAGUAGG CUGAUGAG X CGAA AGGAGGGC		GCCCTCCT T CCTACTCA	
1090	CUGAGUAG CUGAUGAG X CGAA AAGGAGGG		CCCTCCTT C CTACTCAG	
1093	GAGCUGAG CUGAUGAG X CGAA AGGAAGGA		TCCTTCCT A CTCAGCTC	
1096	AGAGAGCU CUGAUGAG X CGAA AGUAGGAA		TTCCTACT C AGCTCTCT	
1101	GCCUCAGA CUGAUGAG X CGAA AGCUGAGU		ACTCAGCT C TCTGAGGC	
1103	GGGCCUCA CUGAUGAG X CGAA AGAGCUGA		TCAGCTCT C TGAGGCCC	
1127	GAGCCUCC CUGAUGAG X CGAA AGCGCCAG		CTGGCGCT C GGAGGCTC	
1135	GUCUCCAC CUGAUGAG X CGAA AGCCUCCG		CGGAGGCT C GTGGAGAC	
1147	CCCAGAAA CUGAUGAG X CGAA AUGGUCUC		GAGACCAT C TTTCTGGG	
1149	AACCCAGA CUGAUGAG X CGAA AGAUGGUC		GACCATCT T TCTGGGTT	
1150	GAACCCAG CUGAUGAG X CGAA AAGAUGGU		ACCATCTT T CTGGGTTC	
1151	GGAACCCA CUGAUGAG X CGAA AAAGAUGG		CCATCTTT C TGGGTTCC	
1157	GGGCCUGG CUGAUGAG X CGAA ACCCAGAA		TTCTGGGT T CCAGGCCC	
1158	AGGGCCUG CUGAUGAG X CGAA AACCCAGA		TCTGGGTT C CAGGCCCT	
1181	CCUGCGGG CUGAUGAG X CGAA AGUCCCUG		CAGGGACT C CCCGCAGG	
1191	GGCGGGGC CUGAUGAG X CGAA ACCUGCGG		CCGCAGGT T GCCCCGCC	
1212	UUUGCCAG CUGAUGAG X CGAA AGCGCUGG		CCAGCGCT A CTGGCAAA	
1233	GCUCCAGA CUGAUGAG X CGAA ACAGGGGC		GCCCCTGT T TCTGGAGC	
1234	AGCUCCAG CUGAUGAG X CGAA AACAGGGG		CCCCTGTT T CTGGAGCT	
1235	CAGCUCCA CUGAUGAG X CGAA AAACAGGG		CCCTGTTT C TGGAGCTG	
1246	UGGUUCCC CUGAUGAG X CGAA AGCAGCUC		GAGCTGCT T GGGAACCA	
1269	GCACCCCG CUGAUGAG X CGAA AGGGGCAC		GTGCCCCT A CGGGGTGC	
1279	GUCUUGAG CUGAUGAG X CGAA AGCACCCC		GGGGTGCT C CTCAAGAC	
1282	UGCGUCUU CUGAUGAG X CGAA AGGAGCAC		GTGCTCCT C AAGACGCA	
1312	GCUGGGGU CUGAUGAG X CGAA ACCGCAGC		GCTGCGGT C ACCCCAGC	
1330	CGGGCACA CUGAUGAG X CGAA ACACCGGC		GCCGGTGT C TGTGCCCG	
1356	CCGCCACA CUGAUGAG X CGAA AGCCCUGG		CCAGGGCT C TGTGGCGG	

Table III

1394	CACCAGGC CUGAUGAG X CGAA ACGGGGGU		ACCCCCGT C GCCTGGTG	
1411	UGCUGGCG CUGAUGAG X CGAA AGCAGCUG		CAGCTGCT C CGCCAGCA	
1440	CGAAGCCG CUGAUGAG X CGAA ACACCUGC		GCAGGTGT A CGGCTTCG	
1446	CCCGCACG CUGAUGAG X CGAA AGCCGUAC		GTACGGCT T CGTGCGGG	
1447	GCCCGCAC CUGAUGAG X CGAA AAGCCGUA		TACGGCTT C GTGCGGGC	
1486	GAGCCCCA CUGAUGAG X CGAA AGGCCUGG		CCAGGCCT C TGGGGCTC	
1494	UGUGCCUG CUGAUGAG X CGAA AGCCCCAG		CTGGGGCT C CAGGCACA	
1515	UCCUGAGG CUGAUGAG X CGAA AGCGGCGU		ACGCCGCT T CCTCAGGA	
1516	UUCCUGAG CUGAUGAG X CGAA AAGCGGCG		CGCCGCTT C CTCAGGAA	
1519	GUGUUCCU CUGAUGAG X CGAA AGGAAGCG		CGCTTCCT C AGGAACAC	
1536	GGGAGAUG CUGAUGAG X CGAA ACUUCUUG		CAAGAAGT T CATCTCCC	
1537	AGGGAGAU CUGAUGAG X CGAA AACUUCUU		AAGAAGTT C ATCTCCCT	
1540	CCCAGGGA CUGAUGAG X CGAA AUGAACUU		AAGTTCAT C TCCCTGGG	
1542	UCCCCAGG CUGAUGAG X CGAA AGAUGAAC		GTTCATCT C CCTGGGGA	
1564	UGCAGCGA CUGAUGAG X CGAA AGCUUGGC		GCCAAGCT C TCGCTGCA	
1566	CCUGCAGC CUGAUGAG X CGAA AGAGCUUG		CAAGCTCT C GCTGCAGG	
1610	GCGCAGCC CUGAUGAG X CGAA AGCGCAGU		ACTGCGCT T GGCTGCGC	
1633	ACACAGCC CUGAUGAG X CGAA ACCCCUGG		CCAGGGGT T GGCTGTGT	
1642	GCGGCCGG CUGAUGAG X CGAA ACACAGCC		GGCTGTGT T CCGGCCGC	
1643	UGCGGCCG CUGAUGAG X CGAA AACACAGC		GCTGTGTT C CGGCCGCA	
1661	CUCACGCA CUGAUGAG X CGAA ACGGUGCU		AGCACCGT C TGCGTGAG	
1675	UUGGCCAG CUGAUGAG X CGAA AUCUCCUC		GAGGAGAT C CTGGCCAA	
1686	AGUGCAGG CUGAUGAG X CGAA ACUUGGCC		GGCCAAGT T CCTGCACT	
1687	CAGUGCAG CUGAUGAG X CGAA AACUUGGC		GCCAAGTT C CTGCACTG	
1710	CGACGACG CUGAUGAG X CGAA ACACACUC		GAGTGTGT A CGTCGTCG	
1714	AGCUCGAC CUGAUGAG X CGAA ACGUACAC		GTGTACGT C GTCGAGCT	
1717	AGCAGCUC CUGAUGAG X CGAA ACGACGUA		TACGTCGT C GAGCTGCT	
1726	AAAGACCU CUGAUGAG X CGAA AGCAGCUC		GAGCTGCT C AGGTCTTT	
1731	AAAAGAAA CUGAUGAG X CGAA ACCUGAGC		GCTCAGGT C TTTCTTTT	
1733	AUAAAAGA CUGAUGAG X CGAA AGACCUGA		TCAGGTCT T TCTTTTAT	
1734	CAUAAAAG CUGAUGAG X CGAA AAGACCUG		CAGGTCTT T CTTTTATG	
1735	ACAUAAAA CUGAUGAG X CGAA AAAGACCU		AGGTCTTT C TTTTATGT	
1737	UGACAUAA CUGAUGAG X CGAA AGAAAGAC		GTCTTTCT T TTATGTCA	
1738	GUGACAUA CUGAUGAG X CGAA AAGAAAGA		TCTTTCTT T TATGTCAC	
1739	CGUGACAU CUGAUGAG X CGAA AAAGAAAG		CTTTCTTT T ATGTCACG	
1740	CCGUGACA CUGAUGAG X CGAA AAAAGAAA		TTTCTTTT A TGTCACGG	
1744	GUCUCCGU CUGAUGAG X CGAA ACAUAAAA		TTTTATGT C ACGGAGAC	
1758	UCUUUUGA CUGAUGAG X CGAA ACGUGGUC		GACCACGT T TCAAAAGA	
1759	UUCUUUUG CUGAUGAG X CGAA AACGUGGU		ACCACGTT T CAAAAGAA	
1760	GUUCUUUU CUGAUGAG X CGAA AAACGUGG		CCACGTTT C AAAAGAAC	
1774	UAGAAAAA CUGAUGAG X CGAA AGCCUGUU		AACAGGCT C TTTTTCTA	
1776	GGUAGAAA CUGAUGAG X CGAA AGAGCCUG		CAGGCTCT T TTTCTACC	
1777	CGGUAGAA CUGAUGAG X CGAA AAGAGCCU		AGGCTCTT T TTCTACCG	
1778	CCGGUAGA CUGAUGAG X CGAA AAAGAGCC		GGCTCTTT T TCTACCGG	
1779	UCCGGUAG CUGAUGAG X CGAA AAAAGAGC		GCTCTTTT T CTACCGGA	
1780	UUCCGGUA CUGAUGAG X CGAA AAAAAGAG		CTCTTTTT C TACCGGAA	
1782	UCUUCCGG CUGAUGAG X CGAA AGAAAAAG		CTTTTTCT A CCGGAAGA	

Table III

1795	UUGCUCCA CUGAUGAG X CGAA ACACUCUU		AAGAGTGT C TGGAGCAA	
1806	UGCUUUGC CUGAUGAG X CGAA ACUUGCUC		GAGCAAGT T GCAAAGCA	
1816	CUGAUUCC CUGAUGAG X CGAA AUGCUUUG		CAAAGCAT T GGAATCAG	
1822	UGCUGUCU CUGAUGAG X CGAA AUUCCAAU		ATTGGAAT C AGACAGCA	
1833	CCCUCUUC CUGAUGAG X CGAA AGUGCUGU		ACAGCACT T GAAGAGGG	
1860	CUGCUUCC CUGAUGAG X CGAA ACAGCUCC		GGAGCTGT C GGAAGCAG	
1873	UGCUGCCU CUGAUGAG X CGAA ACCUCUGC		GCAGAGGT C AGGCAGCA	
1883	GGCUUCCC CUGAUGAG X CGAA AUGCUGCC		GGCAGCAT C GGGAAGCC	
1911	GGAGUCUG CUGAUGAG X CGAA ACGUCAGC		GCTGACGT C CAGACTCC	
1918	AUGAAGCG CUGAUGAG X CGAA AGUCUGGA		TCCAGACT C CGCTTCAT	
1923	UGGGGAUG CUGAUGAG X CGAA AGCGGAGU		ACTCCGCT T CATCCCCA	
1924	UUGGGGAU CUGAUGAG X CGAA AAGCGGAG		CTCCGCTT C ATCCCCAA	
1927	GGCUUGGG CUGAUGAG X CGAA AUGAAGCG		CGCTTCAT C CCCAAGCC	
1954	AUGUUCAC CUGAUGAG X CGAA AUCGGCCG		CGGCCGAT T GTGAACAT	
1968	CCACGACG CUGAUGAG X CGAA AGUCCAUG		CATGGACT A CGTCGTGG	
1972	GCUCCCAC CUGAUGAG X CGAA ACGUAGUC		GACTACGT C GTGGGAGC	
1989	CUCUGCGG CUGAUGAG X CGAA ACGUUCUG		CAGAACGT T CCGCAGAG	
1990	UCUCUGCG CUGAUGAG X CGAA AACGUUCU		AGAACGTT C CGCAGAGA	
2015	CGAGGUGA CUGAUGAG X CGAA ACGCUCGG		CCGAGCGT C TCACCTCG	
2017	CUCGAGGU CUGAUGAG X CGAA AGACGCUC		GAGCGTCT C ACCTCGAG	
2022	UCACCCUC CUGAUGAG X CGAA AGGUGAGA		TCTCACCT C GAGGGTGA	
2040	GCACGCUG CUGAUGAG X CGAA ACAGUGCC		GGCACTGT T CAGCGTGC	
2041	AGCACGCU CUGAUGAG X CGAA AACAGUGC		GCACTGTT C AGCGTGCT	
2050	UCGUAGUU CUGAUGAG X CGAA AGCACGCU		AGCGTGCT C AACTACGA	
2055	CCCGCUCG CUGAUGAG X CGAA AGUUGAGC		GCTCAACT A CGAGCGGG	
2080	GCGCCCAG CUGAUGAG X CGAA AGGCCGGG		CCCGGCCT C CTGGGCGC	
2091	CCAGCACA CUGAUGAG X CGAA AGGCGCCC		GGGCGCCT C TGTGCTGG	
2111	CCUGUGGA CUGAUGAG X CGAA AUCGUCCA		TGGACGAT A TCCACAGG	
2113	GCCCUGUG CUGAUGAG X CGAA AUAUCGUC		GACGATAT C CACAGGGC	
2133	GCAGCACG CUGAUGAG X CGAA AGGUGCGC		GCGCACCT T CGTGCTGC	
2134	CGCAGCAC CUGAUGAG X CGAA AAGGUGCG		CGCACCTT C GTGCTGCG	
2175	UGACAAAG CUGAUGAG X CGAA ACAGCUCA		TGAGCTGT A CTTTGTCA	
2178	CCUUGACA CUGAUGAG X CGAA AGUACAGC		GCTGTACT T TGTCAAGG	
2179	ACCUUGAC CUGAUGAG X CGAA AAGUACAG		CTGTACTT T GTCAAGGT	
2182	UCCACCUU CUGAUGAG X CGAA ACAAAGUA		TACTTTGT C AAGGTGGA	
2205	UGGUGUCG CUGAUGAG X CGAA ACGCGCCC		GGGCGCGT A CGACACCA	
2215	UCCUGGGG CUGAUGAG X CGAA AUGGUGUC		GACACCAT C CCCCAGGA	
2230	ACCUCCGU CUGAUGAG X CGAA AGCCUGUC		GACAGGCT C ACGGAGGT	
2239	CUGGCGAU CUGAUGAG X CGAA ACCUCCGU		ACGGAGGT C ATCGCCAG	
2242	AUGCUGGC CUGAUGAG X CGAA AUGACCUC		GAGGTCAT C GCCAGCAT	
2251	GGUUUGAU CUGAUGAG X CGAA AUGCUGGC		GCCAGCAT C ATCAAACC	
2254	UGGGGUUU CUGAUGAG X CGAA AUGAUGCU		AGCATCAT C AAACCCCA	
2271	GCACGCAG CUGAUGAG X CGAA ACGUGUUC		GAACACGT A CTGCGTGC	
2282	GGCAUACC CUGAUGAG X CGAA ACGCACGC		GCGTGCGT C GGTATGCC	
2286	CCACGGCA CUGAUGAG X CGAA ACCGACGC		GCGTCGGT A TGCCGTGG	
2296	GCCUUCUG CUGAUGAG X CGAA ACCACGGC		GCCGTGGT C CAGAAGGC	
2320	GCCUUGCG CUGAUGAG X CGAA ACGUGCCC		GGGCACGT C CGCAAGGC	

Table III

2331	GGCUCUUG CUGAUGAG X CGAA AGGCCUUG		CAAGGCCT T CAAGAGCC	
2332	UGGCUCUU CUGAUGAG X CGAA AAGGCCUU		AAGGCCTT C AAGAGCCA	
2344	AAGGUAGA CUGAUGAG X CGAA ACGUGGCU		AGCCACGT C TCTACCTT	
2346	UCAAGGUA CUGAUGAG X CGAA AGACGUGG		CCACGTCT C TACCTTGA	
2348	UGUCAAGG CUGAUGAG X CGAA AGAGACGU		ACGTCTCT A CCTTGACA	
2352	GGUCUGUC CUGAUGAG X CGAA AGGUAGAG		CTCTACCT T GACAGACC	
2362	UACGGCUG CUGAUGAG X CGAA AGGUCUGU		ACAGACCT C CAGCCGTA	
2370	GUCGCAUG CUGAUGAG X CGAA ACGGCUGG		CCAGCCGT A CATGCGAC	
2382	GAGCCACG CUGAUGAG X CGAA ACUGUCGC		GCGACAGT T CGTGGCTC	
2383	UGAGCCAC CUGAUGAG X CGAA AACUGUCG		CGACAGTT C GTGGCTCA	
2390	CUGCAGGU CUGAUGAG X CGAA AGCCACGA		TCGTGGCT C ACCTGCAG	
2425	UCGAUGAC CUGAUGAG X CGAA ACGGCAUC		GATGCCGT C GTCATCGA	
2428	UGCUCGAU CUGAUGAG X CGAA ACGACGGC		GCCGTCGT C ATCGAGCA	
2431	CUCUGCUC CUGAUGAG X CGAA AUGACGAC		GTCGTCAT C GAGCAGAG	
2442	UCAGGGAG CUGAUGAG X CGAA AGCUCUGC		GCAGAGCT C CTCCCTGA	
2445	CAUUCAGG CUGAUGAG X CGAA AGGAGCUC		GAGCTCCT C CCTGAATG	
2470	ACGUCGAA CUGAUGAG X CGAA AGGCCACU		AGTGGCCT C TTCGACGT	
2472	AGACGUCG CUGAUGAG X CGAA AGAGGCCA		TGGCCTCT T CGACGTCT	
2473	AAGACGUC CUGAUGAG X CGAA AAGAGGCC		GGCCTCTT C GACGTCTT	
2479	CGUAGGAA CUGAUGAG X CGAA ACGUCGAA		TTCGACGT C TTCCTACG	
2481	AGCGUAGG CUGAUGAG X CGAA AGACGUCG		CGACGTCT T CCTACGCT	
2482	AAGCGUAG CUGAUGAG X CGAA AAGACGUC		GACGTCTT C CTACGCTT	
2485	AUGAAGCG CUGAUGAG X CGAA AGGAAGAC		GTCTTCCT A CGCTTCAT	
2490	GGCACAUG CUGAUGAG X CGAA AGCGUAGG		CCTACGCT T CATGTGCC	
2491	UGGCACAU CUGAUGAG X CGAA AAGCGUAG		CTACGCTT C ATGTGCCA	
2515	UUGCCCCU CUGAUGAG X CGAA AUGCGCAC		GTGCGCAT C AGGGGCAA	
2526	GGACGUAG CUGAUGAG X CGAA ACUUGCCC		GGGCAAGT C CTACGTCC	
2529	ACUGGACG CUGAUGAG X CGAA AGGACUUG		CAAGTCCT A CGTCCAGT	
2533	UGGCACUG CUGAUGAG X CGAA ACGUAGGA		TCCTACGT C CAGTGCCA	
2548	CCCUGCGG CUGAUGAG X CGAA AUCCCCUG		CAGGGGAT C CCGCAGGG	
2559	AGAGGAUG CUGAUGAG X CGAA AGCCCUGC		GCAGGGCT C CATCCTCT	
2563	GUGGAGAG CUGAUGAG X CGAA AUGGAGCC		GGCTCCAT C CTCTCCAC	
2566	AGCGUGGA CUGAUGAG X CGAA AGGAUGGA		TCCATCCT C TCCACGCT	
2568	GCAGCGUG CUGAUGAG X CGAA AGAGGAUG		CATCCTCT C CACGCTGC	
2578	AGGCUGCA CUGAUGAG X CGAA AGCAGCGU		ACGCTGCT C TGCAGCCT	
2592	UGUCGCCG CUGAUGAG X CGAA AGCACAGG		CCTGTGCT A CGGCGACA	
2616	UCCCCGCA CUGAUGAG X CGAA ACAGCUUG		CAAGCTGT T TGCGGGGA	
2617	AUCCCCGC CUGAUGAG X CGAA AACAGCUU		AAGCTGTT T GCGGGGAT	
2626	UCCCGCCG CUGAUGAG X CGAA AUCCCCGC		GCGGGGAT T CGGCGGGA	
2627	GUCCCGCC CUGAUGAG X CGAA AAUCCCCG		CGGGGATT C GGCGGGAC	
2644	AAACGCAG CUGAUGAG X CGAA AGCAGCCC		GGGCTGCT C CTGCGTTT	
2651	AUCCACCA CUGAUGAG X CGAA ACGCAGGA		TCCTGCGT T TGGTGGAT	
2652	CAUCCACC CUGAUGAG X CGAA AACGCAGG		CCTGCGTT T GGTGGATG	
2663	CAACAAGA CUGAUGAG X CGAA AUCAUCCA		TGGATGAT T TCTTGTTG	
2664	CCAACAAG CUGAUGAG X CGAA AAUCAUCC		GGATGATT T CTTGTTGG	
2665	ACCAACAA CUGAUGAG X CGAA AAAUCAUC		GATGATTT C TTGTTGGT	
2667	UCACCAAC CUGAUGAG X CGAA AGAAAUCA		TGATTTCT T GTTGGTGA	

Table III

2670	GUGUCACC CUGAUGAG X CGAA ACAAGAAA		TTTCTTGT T GGTGACAC	
2681	GGUGAGGU CUGAUGAG X CGAA AGGUGUCA		TGACACCT C ACCTCACC	
2686	GCGUGGGU CUGAUGAG X CGAA AGGUGAGG		CCTCACCT C ACCCACGC	
2703	UCCUGAGG CUGAUGAG X CGAA AGGUUUUC		GAAAACCT T CCTCAGGA	
2704	GUCCUGAG CUGAUGAG X CGAA AAGGUUUU		AAAACCTT C CTCAGGAC	
2707	AGGGUCCU CUGAUGAG X CGAA AGGAAGGU		ACCTTCCT C AGGACCCT	
2719	ACACCUCG CUGAUGAG X CGAA ACCAGGGU		ACCCTGGT C CGAGGTGT	
2728	UACUCAGG CUGAUGAG X CGAA ACACCUCG		CGAGGTGT C CCTGAGTA	
2736	CGCAGCCA CUGAUGAG X CGAA ACUCAGGG		CCCTGAGT A TGGCTGCG	
2754	UCUUCCGC CUGAUGAG X CGAA AGUUCACC		GGTGAACT T GCGGAAGA	
2775	CUACAGGG CUGAUGAG X CGAA AGUUCACC		GGTGAACT T CCCTGTAG	
2776	UCUACAGG CUGAUGAG X CGAA AAGUUCAC		GTGAACTT C CCTGTAGA	
2782	UCGUCUUC CUGAUGAG X CGAA ACAGGGAA		TTCCCTGT A GAAGACGA	
2810	CUGAACAA CUGAUGAG X CGAA AGCCGUGC		GCACGGCT T TTGTTCAG	
2811	UCUGAACA CUGAUGAG X CGAA AAGCCGUG		CACGGCTT T TGTTCAGA	
2812	AUCUGAAC CUGAUGAG X CGAA AAAGCCGU		ACGGCTTT T GTTCAGAT	
2815	GGCAUCUG CUGAUGAG X CGAA ACAAAAGC		GCTTTTGT T CAGATGCC	
2816	CGGCAUCU CUGAUGAG X CGAA AACAAAAG		CTTTTGTT C AGATGCCG	
2836	CAGGGGAA CUGAUGAG X CGAA AGGCCGUG		CACGGCCT A TTCCCCTG	
2838	ACCAGGGG CUGAUGAG X CGAA AUAGGCCG		CGGCCTAT T CCCCTGGT	
2839	CACCAGGG CUGAUGAG X CGAA AAUAGGCC		GGCCTATT C CCCTGGTG	
2864	GGUCCGGG CUGAUGAG X CGAA AUCCAGCA		TGCTGGAT A CCCGGACC	
2892	AGCUGGAG CUGAUGAG X CGAA AGUCGCUC		GAGCGACT A CTCCAGCT	
2895	CAUAGCUG CUGAUGAG X CGAA AGUAGUCG		CGACTACT C CAGCTATG	
2901	UCCGGGCA CUGAUGAG X CGAA AGCUGGAG		CTCCAGCT A TGCCCGGA	
2913	CUCUGAUG CUGAUGAG X CGAA AGGUCCGG		CCGGACCT C CATCAGAG	
2917	CUGGCUCU CUGAUGAG X CGAA AUGGAGGU		ACCTCCAT C AGAGCCAG	
2927	GAAGGUGA CUGAUGAG X CGAA ACUGGCUC		GAGCCAGT C TCACCTTC	
2929	UUGAAGGU CUGAUGAG X CGAA AGACUGGC		GCCAGTCT C ACCTTCAA	
2934	CGCGGUUG CUGAUGAG X CGAA AGGUGAGA		TCTCACCT T CAACCGCG	
2935	CCGCGGUU CUGAUGAG X CGAA AAGGUGAG		CTCACCTT C AACCGCGG	
2946	CAGCCUUG CUGAUGAG X CGAA AGCCGCGG		CCGCGGCT T CAAGGCTG	
2947	CCAGCCUU CUGAUGAG X CGAA AAGCCGCG		CGCGGCTT C AAGGCTGG	
2969	GAGUUUGC CUGAUGAG X CGAA ACGCAUGU		ACATGCGT C GCAAACTC	
2977	ACCCCAAA CUGAUGAG X CGAA AGUUUGCG		CGCAAACT C TTTGGGGT	
2979	AGACCCCA CUGAUGAG X CGAA AGAGUUUG		CAAACTCT T TGGGGTCT	
2980	AAGACCCC CUGAUGAG X CGAA AAGAGUUU		AAACTCTT T GGGGTCTT	
2986	AGCCGCAA CUGAUGAG X CGAA ACCCCAAA		TTTGGGGT C TTGCGGCT	
2988	UCAGCCGC CUGAUGAG X CGAA AGACCCCA		TGGGGTCT T GCGGCTGA	
3002	CAGGCUGU CUGAUGAG X CGAA ACACUUCA		TGAAGTGT C ACAGCCTG	
3012	AAUCCAGA CUGAUGAG X CGAA ACAGGCUG		CAGCCTGT T TCTGGATT	
3013	AAAUCCAG CUGAUGAG X CGAA AACAGGCU		AGCCTGTT T CTGGATTT	
3014	CAAAUCCA CUGAUGAG X CGAA AAACAGGC		GCCTGTTT C TGGATTTG	
3020	CACCUGCA CUGAUGAG X CGAA AUCCAGAA		TTCTGGAT T TGCAGGTG	
3021	UCACCUGC CUGAUGAG X CGAA AAUCCAGA		TCTGGATT T GCAGGTGA	
3037	ACCGUCUG CUGAUGAG X CGAA AGGCUGUU		AACAGCCT C CAGACGGT	
3058	AUCUUGUA CUGAUGAG X CGAA AUGUUGGU		ACCAACAT C TACAAGAT	

Table III

3060	GGAUCUUG CUGAUGAG X CGAA AGAUGUUG		CAACATCT A CAAGATCC	
3067	AGCAGGAG CUGAUGAG X CGAA AUCUUGUA		TACAAGAT C CTCCTGCT	
3070	UGCAGCAG CUGAUGAG X CGAA AGGAUCUU		AAGATCCT C CTGCTGCA	
3084	GAAACCUG CUGAUGAG X CGAA ACGCCUGC		GCAGGCGT A CAGGTTTC	
3090	AUGCGUGA CUGAUGAG X CGAA ACCUGUAC		GTACAGGT T TCACGCAT	
3091	CAUGCGUG CUGAUGAG X CGAA AACCUGUA		TACAGGTT T CACGCATG	
3092	ACAUGCGU CUGAUGAG X CGAA AAACCUGU		ACAGGTTT C ACGCATGT	
3112	UGAAAUGG CUGAUGAG X CGAA AGCUGCAG		CTGCAGCT C CCATTTCA	
3117	GCUGAUGA CUGAUGAG X CGAA AUGGGAGC		GCTCCCAT T TCATCAGC	
3118	UGCUGAUG CUGAUGAG X CGAA AAUGGGAG		CTCCCATT T CATCAGCA	
3119	UUGCUGAU CUGAUGAG X CGAA AAAUGGGA		TCCCATTT C ATCAGCAA	
3122	AACUUGCU CUGAUGAG X CGAA AUGAAAUG		CATTTCAT C AGCAAGTT	
3130	UUCUUCCA CUGAUGAG X CGAA ACUUGCUG		CAGCAAGT T TGGAAGAA	
3131	GUUCUUCC CUGAUGAG X CGAA AACUUGCU		AGCAAGTT T GGAAGAAC	
3147	GCAGGAAA CUGAUGAG X CGAA AUGUGGGG		CCCCACAT T TTTCCTGC	
3148	CGCAGGAA CUGAUGAG X CGAA AAUGUGGG		CCCACATT T TTCCTGCG	
3149	GCGCAGGA CUGAUGAG X CGAA AAAUGUGG		CCACATTT T TCCTGCGC	
3150	CGCGCAGG CUGAUGAG X CGAA AAAAUGUG		CACATTTT T CCTGCGCG	
3151	ACGCGCAG CUGAUGAG X CGAA AAAAAUGU		ACATTTTT C CTGCGCGT	
3160	UCAGAGAU CUGAUGAG X CGAA ACGCGCAG		CTGCGCGT C ATCTCTGA	
3163	GUGUCAGA CUGAUGAG X CGAA AUGACGCG		CGCGTCAT C TCTGACAC	
3165	CCGUGUCA CUGAUGAG X CGAA AGAUGACG		CGTCATCT C TGACACGG	
3177	AGCAGAGG CUGAUGAG X CGAA AGGCCGUG		CACGGCCT C CCTCTGCT	
3181	GAGUAGCA CUGAUGAG X CGAA AGGGAGGC		GCCTCCCT C TGCTACTC	
3186	GGAUGGAG CUGAUGAG X CGAA AGCAGAGG		CCTCTGCT A CTCCATCC	
3189	UCAGGAUG CUGAUGAG X CGAA AGUAGCAG		CTGCTACT C CATCCTGA	
3193	GCUUUCAG CUGAUGAG X CGAA AUGGAGUA		TACTCCAT C CTGAAAGC	
3219	CCCCCAGC CUGAUGAG X CGAA ACAUCCCU		AGGGATGT C GCTGGGGG	
3248	GGAGGGCA CUGAUGAG X CGAA AGGGCCGG		CCGGCCCT C TGCCCTCC	
3255	CGGCCUCG CUGAUGAG X CGAA AGGGCAGA		TCTGCCCT C CGAGGCCG	
3288	UGAGCAGG CUGAUGAG X CGAA AUGCUUGG		CCAAGCAT T CCTGCTCA	
3289	UUGAGCAG CUGAUGAG X CGAA AAUGCUUG		CAAGCATT C CTGCTCAA	
3295	GUCAGCUU CUGAUGAG X CGAA AGCAGGAA		TTCCTGCT C AAGCTGAC	
3305	ACGGUGUC CUGAUGAG X CGAA AGUCAGCU		AGCTGACT C GACACCGT	
3316	ACGUAGGU CUGAUGAG X CGAA ACACGGUG		CACCGTGT C ACCTACGT	
3321	GUGGCACG CUGAUGAG X CGAA AGGUGACA		TGTCACCT A CGTGCCAC	
3331	GACCCCAG CUGAUGAG X CGAA AGUGGCAC		GTGCCACT C CTGGGGTC	
3339	UCCUGAGU CUGAUGAG X CGAA ACCCCAGG		CCTGGGGT C ACTCAGGA	
3343	GCUGUCCU CUGAUGAG X CGAA AGUGACCC		GGGTCACT C AGGACAGC	
3368	GAGCUUCC CUGAUGAG X CGAA ACUCAGCU		AGCTGAGT C GGAAGCTC	
3376	GUCCCCGG CUGAUGAG X CGAA AGCUUCCG		CGGAAGCT C CCGGGGAC	
3429	UGAAGUCU CUGAUGAG X CGAA AGGGCAGU		ACTGCCCT C AGACTTCA	
3435	UGGUCUUG CUGAUGAG X CGAA AGUCUGAG		CTCAGACT T CAAGACCA	
3436	AUGGUCUU CUGAUGAG X CGAA AAGUCUGA		TCAGACTT C AAGACCAT	
3445	CAGUCCAG CUGAUGAG X CGAA AUGGUCUU		AAGACCAT C CTGGACTG	
3503	CCCGGCGU CUGAUGAG X CGAA ACAGGGCU		AGCCCTGT C ACGCCGGG	
3514	GGGACGUA CUGAUGAG X CGAA AGCCCGGC		GCCGGGCT C TACGTCCC	

Table III

3516	CUGGGACG CUGAUGAG X CGAA AGAGCCCG		CGGGCTCT A CGTCCCAG	
3520	CUCCCUGG CUGAUGAG X CGAA ACGUAGAG		CTCTACGT C CCAGGGAG	
3568	AGGCCUCA CUGAUGAG X CGAA ACUCCCAG		CTGGGAGT C TGAGGCCT	
3587	CUCGGCCA CUGAUGAG X CGAA ACACUCAC		GTGAGTGT T TGGCCGAG	
3588	CCUCGGCC CUGAUGAG X CGAA AACACUCA		TGAGTGTT T GGCCGAGG	
3606	UUCAGCCG CUGAUGAG X CGAA ACAUGCAG		CTGCATGT C CGGCTGAA	
3625	CUCAGCCG CUGAUGAG X CGAA ACACUCAG		CTGAGTGT C CGGCTGAG	
3648	CUUGGCUG CUGAUGAG X CGAA ACACUCGC		GCGAGTGT C CAGCCAAG	
3667	GUGUGCUG CUGAUGAG X CGAA ACACUCAG		CTGAGTGT C CAGCACAC	
3683	GAAGUGAA CUGAUGAG X CGAA ACGGCAGG		CCTGCCGT C TTCACTTC	
3685	GGGAAGUG CUGAUGAG X CGAA AGACGGCA		TGCCGTCT T CACTTCCC	
3686	GGGGAAGU CUGAUGAG X CGAA AAGACGGC		GCCGTCTT C ACTTCCCC	
3690	CUGUGGGG CUGAUGAG X CGAA AGUGAAGA		TCTTCACT T CCCCACAG	
3691	CCUGUGGG CUGAUGAG X CGAA AAGUGAAG		CTTCACTT C CCCACAGG	
3708	GUGGAGCC CUGAUGAG X CGAA AGCGCCAG		CTGGCGCT C GGCTCCAC	
3713	CUGGGGUG CUGAUGAG X CGAA AGCCGAGC		GCTCGGCT C CACCCCAG	
3730	GUGAGGAA CUGAUGAG X CGAA AGCUGGCC		GGCCAGCT T TTCCTCAC	
3731	GGUGAGGA CUGAUGAG X CGAA AAGCUGGC		GCCAGCTT T TCCTCACC	
3732	UGGUGAGG CUGAUGAG X CGAA AAAGCUGG		CCAGCTTT T CCTCACCA	
3733	CUGGUGAG CUGAUGAG X CGAA AAAAGCUG		CAGCTTTT C CTCACCAG	
3736	CUCCUGGU CUGAUGAG X CGAA AGGAAAAG		CTTTTCCT C ACCAGGAG	
3752	GGGAGUGG CUGAUGAG X CGAA AGCCGGGC		GCCCGGCT T CCACTCCC	
3753	GGGGAGUG CUGAUGAG X CGAA AAGCCGGG		CCCGGCTT C CACTCCCC	
3758	UAUGUGGG CUGAUGAG X CGAA AGUGGAAG		CTTCCACT C CCCACATA	
3766	ACUAUUCC CUGAUGAG X CGAA AUGUGGGG		CCCCACAT A GGAATAGT	
3772	GGAUGGAC CUGAUGAG X CGAA AUUCCUAU		ATAGGAAT A GTCCATCC	
3775	UGGGGAUG CUGAUGAG X CGAA ACUAUUCC		GGAATAGT C CATCCCCA	
3779	AAUCUGGG CUGAUGAG X CGAA AUGGACUA		TAGTCCAT C CCCAGATT	
3787	CAAUGGCG CUGAUGAG X CGAA AUCUGGGG		CCCCAGAT T CGCCATTG	
3788	ACAAUGGC CUGAUGAG X CGAA AAUCUGGG		CCCAGATT C GCCATTGT	
3794	GGGUGAAC CUGAUGAG X CGAA AUGGCGAA		TTCGCCAT T GTTCACCC	
3797	GAGGGGUG CUGAUGAG X CGAA ACAAUGGC		GCCATTGT T CACCCCTC	
3798	CGAGGGGU CUGAUGAG X CGAA AACAAUGG		CCATTGTT C ACCCCTCG	
3805	GGCAGGGC CUGAUGAG X CGAA AGGGGUGA		TCACCCCT C GCCCTGCC	
3816	AGGCAAAG CUGAUGAG X CGAA AGGGCAGG		CCTGCCCT C CTTTGCCT	
3819	GGAAGGCA CUGAUGAG X CGAA AGGAGGGC		GCCCTCCT T TGCCTTCC	
3820	UGGAAGGC CUGAUGAG X CGAA AAGGAGGG		CCCTCCTT T GCCTTCCA	
3825	GGGGGUGG CUGAUGAG X CGAA AGGCAAAG		CTTTGCCT T CCACCCCC	
3826	UGGGGGUG CUGAUGAG X CGAA AAGGCAAA		TTTGCCTT C CACCCCCA	
3839	UCCACCUG CUGAUGAG X CGAA AUGGUGGG		CCCACCAT C CAGGTGGA	
3873	AAUUCCCA CUGAUGAG X CGAA AGCUCCCA		TGGGAGCT C TGGGAATT	
3881	UCACUCCA CUGAUGAG X CGAA AUUCCCAG		CTGGGAAT T TGGAGTGA	
3882	GUCACUCC CUGAUGAG X CGAA AAUUCCCA		TGGGAATT T GGAGTGAC	
3907	CGCCUGUG CUGAUGAG X CGAA ACAGGGCA		TGCCCTGT A CACAGGCG	
3940	CCCACAGG CUGAUGAG X CGAA ACCCCCAU		ATGGGGGT C CCTGTGGG	
3950	CCCAAUUU CUGAUGAG X CGAA ACCCACAG		CTGTGGGT C AAATTGGG	
3955	CUCCCCCC CUGAUGAG X CGAA AUUUGACC		GGTCAAAT T GGGGGGAG	

Table III

3977	CAGUAUUU CUGAUGAG X CGAA ACUCCCAC		GTGGGAGT A AAATACTG	
3982	AUAUUCAG CUGAUGAG X CGAA AUUUUACU		AGTAAAAT A CTGAATAT	
3989	AACUCAUA CUGAUGAG X CGAA AUUCAGUA		TACTGAAT A TATGAGTT	
3991	AAAACUCA CUGAUGAG X CGAA AUAUUCAG		CTGAATAT A TGAGTTTT	
3997	AACUGAAA CUGAUGAG X CGAA ACUCAUAU		ATATGAGT T TTTCAGTT	
3998	AAACUGAA CUGAUGAG X CGAA AACUCAUA		TATGAGTT T TTCAGTTT	
3999	AAAACUGA CUGAUGAG X CGAA AAACUCAU		ATGAGTTT T TCAGTTTT	
4000	CAAAACUG CUGAUGAG X CGAA AAAACUCA		TGAGTTTT T CAGTTTTG	
4001	UCAAAACU CUGAUGAG X CGAA AAAAACUC		GAGTTTTT C AGTTTTGA	
4005	UUUUUCAA CUGAUGAG X CGAA ACUGAAAA		TTTTCAGT T TTGAAAAA	
4006	UUUUUUCA CUGAUGAG X CGAA AACUGAAA		TTTCAGTT T TGAAAAAA	
4007	UUUUUUUC CUGAUGAG X CGAA AAACUGAA		TTCAGTTT T GAAAAAAA	

Stem Length = 8 . Core Sequence = CUGAUGAG X CGAA (X = GCCGUUAGGC or other stem II sequence and length (greater than or equal to 2 base-pairs))
Seq1 = TERT (Homo sapiens telomerase reverse transcriptase (TERT) mRNA, 4015 bp); Nakamura *et al.*, Science 277 (5328), 955-959 (1997)

Table IV: Human telomerase reverse transcriptase (TERT) NCH Ribozyme and Target Sequence

nt. Position	Ribozyme Sequence	Seq ID Nos	Substrate Sequence	Seq ID Nos
14	GCGCAGCA CUGAUGAG X CGAA IACGCAGC		GCTGCGTC C TGCTGCGC	
15	UGCGCAGC CUGAUGAG X CGAA IGACGCAG		CTGCGTCC T GCTGCGCA	
18	ACGUGCGC CUGAUGAG X CGAA ICAGGACG		CGTCCTGC T GCGCACGT	
23	UUCCCACG CUGAUGAG X CGAA ICGCAGCA		TGCTGCGC A CGTGGGAA	
34	GGGGCCAG CUGAUGAG X CGAA ICUUCCCA		TGGGAAGC C CTGGCCCC	
35	CGGGGCCA CUGAUGAG X CGAA IGCUUCCC		GGGAAGCC C TGGCCCCG	
36	CCGGGGCC CUGAUGAG X CGAA IGGCUUCC		GGAAGCCC T GGCCCCGG	
40	GUGGCCGG CUGAUGAG X CGAA ICCAGGGC		GCCCTGGC C CCGGCCAC	
41	GGUGGCCG CUGAUGAG X CGAA IGCCAGGG		CCCTGGCC C CGGCCACC	
42	GGGUGGCC CUGAUGAG X CGAA IGGCCAGG		CCTGGCCC C GGCCACCC	
46	GCGGGGGU CUGAUGAG X CGAA ICCGGGGC		GCCCCGGC C ACCCCCGC	
47	CGCGGGGG CUGAUGAG X CGAA IGCCGGGG		CCCCGGCC A CCCCCGCG	
49	AUCGCGGG CUGAUGAG X CGAA IUGGCCGG		CCGGCCAC C CCCGCGAT	
50	CAUCGCGG CUGAUGAG X CGAA IGUGGCCG		CGGCCACC C CCGCGATG	
51	GCAUCGCG CUGAUGAG X CGAA IGGUGGCC		GGCCACCC C CGCGATGC	
52	GGCAUCGC CUGAUGAG X CGAA IGGGUGGC		GCCACCCC C GCGATGCC	
60	GAGCGCGC CUGAUGAG X CGAA ICAUCGCG		CGCGATGC C GCGCGCTC	
67	CAGCGGGG CUGAUGAG X CGAA ICGCGCGG		CCGCGCGC T CCCCGCTG	
69	GGCAGCGG CUGAUGAG X CGAA IAGCGCGC		GCGCGCTC C CCGCTGCC	
70	CGGCAGCG CUGAUGAG X CGAA IGAGCGCG		CGCGCTCC C CGCTGCCG	
71	UCGGCAGC CUGAUGAG X CGAA IGGAGCGC		GCGCTCCC C GCTGCCGA	
74	GGCUCGGC CUGAUGAG X CGAA ICGGGGAG		CTCCCCGC T GCCGAGCC	
77	CACGGCUC CUGAUGAG X CGAA ICAGCGGG		CCCGCTGC C GAGCCGTG	
82	GAGCGCAC CUGAUGAG X CGAA ICUCGGCA		TGCCGAGC C GTGCGCTC	
89	CAGCAGGG CUGAUGAG X CGAA ICGCACGG		CCGTGCGC T CCCTGCTG	
91	CGCAGCAG CUGAUGAG X CGAA IAGCGCAC		GTGCGCTC C CTGCTGCG	
92	GCGCAGCA CUGAUGAG X CGAA IGAGCGCA		TGCGCTCC C TGCTGCGC	
93	UGCGCAGC CUGAUGAG X CGAA IGGAGCGC		GCGCTCCC T GCTGCGCA	
96	GGCUGCGC CUGAUGAG X CGAA ICAGGGAG		CTCCCTGC T GCGCAGCC	
101	GUAGUGGC CUGAUGAG X CGAA ICGCAGCA		TGCTGCGC A GCCACTAC	
104	GCGGUAGU CUGAUGAG X CGAA ICUGCGCA		TGCGCAGC C ACTACCGC	
105	CGCGGUAG CUGAUGAG X CGAA IGCUGCGC		GCGCAGCC A CTACCGCG	
107	CUCGCGGU CUGAUGAG X CGAA IUGGCUGC		GCAGCCAC T ACCGCGAG	
110	CACCUCGC CUGAUGAG X CGAA IUAGUGGC		GCCACTAC C GCGAGGTG	
120	CCAGCGGC CUGAUGAG X CGAA ICACCUCG		CGAGGTGC T GCCGCTGG	
123	UGGCCAGC CUGAUGAG X CGAA ICAGCACC		GGTGCTGC C GCTGGCCA	
126	ACGUGGCC CUGAUGAG X CGAA ICGGCAGC		GCTGCCGC T GGCCACGT	
130	ACGAACGU CUGAUGAG X CGAA ICCAGCGG		CCGCTGGC C ACGTTCGT	
131	CACGAACG CUGAUGAG X CGAA IGCCAGCG		CGCTGGCC A CGTTCGTG	
146	GGGCCCCA CUGAUGAG X CGAA ICGCCGCA		TGCGGCGC C TGGGGCCC	
147	GGGGCCCC CUGAUGAG X CGAA IGCGCCGC		GCGGCGCC T GGGGCCCC	
153	AGCCCUGG CUGAUGAG X CGAA ICCCCAGG		CCTGGGGC C CCAGGGCT	
154	CAGCCCUG CUGAUGAG X CGAA IGCCCCAG		CTGGGGCC C CAGGGCTG	

Table IV

155	CCAGCCCU CUGAUGAG X CGAA IGGCCCCA		TGGGGCCC C AGGGCTGG	
156	GCCAGCCC CUGAUGAG X CGAA IGGGCCCC		GGGGCCCC A GGGCTGGC	
161	CAGCCGCC CUGAUGAG X CGAA ICCCUGGG		CCCAGGGC T GGCGGCTG	
168	GCUGCACC CUGAUGAG X CGAA ICCGCCAG		CTGGCGGC T GGTGCAGC	
174	CCCCGCGC CUGAUGAG X CGAA ICACCAGC		GCTGGTGC A GCGCGGGG	
185	AGCCGCCG CUGAUGAG X CGAA IUCCCCGC		GCGGGGAC C CGGCGGCT	
186	AAGCCGCC CUGAUGAG X CGAA IGUCCCCG		CGGGGACC C GGCGGCTT	
193	GCGCGGAA CUGAUGAG X CGAA ICCGCCGG		CCGGCGGC T TTCCGCGC	
197	CAGCGCGC CUGAUGAG X CGAA IAAAGCCG		CGGCTTTC C GCGCGCTG	
204	GGGCCACC CUGAUGAG X CGAA ICGCGCGG		CCGCGCGC T GGTGGCCC	
211	AGGCACUG CUGAUGAG X CGAA ICCACCAG		CTGGTGGC C CAGTGCCT	
212	CAGGCACU CUGAUGAG X CGAA IGCCACCA		TGGTGGCC C AGTGCCTG	
213	CCAGGCAC CUGAUGAG X CGAA IGGCCACC		GGTGGCCC A GTGCCTGG	
218	GCACACCA CUGAUGAG X CGAA ICACUGGG		CCCAGTGC C TGGTGTGC	
219	CGCACACC CUGAUGAG X CGAA IGCACUGG		CCAGTGCC T GGTGTGCG	
231	CGUCCCAG CUGAUGAG X CGAA ICACGCAC		GTGCGTGC C CTGGGACG	
232	GCGUCCCA CUGAUGAG X CGAA IGCACGCA		TGCGTGCC C TGGGACGC	
233	UGCGUCCC CUGAUGAG X CGAA IGGCACGC		GCGTGCCC T GGGACGCA	
241	GGCGGCCG CUGAUGAG X CGAA ICGUCCCA		TGGGACGC A CGGCCGCC	
246	CGGGGGGC CUGAUGAG X CGAA ICCGUGCG		CGCACGGC C GCCCCCCG	
249	CGGCGGGG CUGAUGAG X CGAA ICGGCCGU		ACGGCCGC C CCCCGCCG	
250	GCGGCGGG CUGAUGAG X CGAA IGCGGCCG		CGGCCGCC C CCCGCCGC	
251	GGCGGCGG CUGAUGAG X CGAA IGGCGGCC		GGCCGCCC C CCGCCGCC	
252	GGGCGGCG CUGAUGAG X CGAA IGGGCGGC		GCCGCCCC C CGCCGCCC	
253	GGGGCGGC CUGAUGAG X CGAA IGGGGCGG		CCGCCCCC C GCCGCCCC	
256	GAGGGGGC CUGAUGAG X CGAA ICGGGGGG		CCCCCCGC C GCCCCCTC	
259	AAGGAGGG CUGAUGAG X CGAA ICGGCGGG		CCCGCCGC C CCCTCCTT	
260	GAAGGAGG CUGAUGAG X CGAA IGCGGCGG		CCGCCGCC C CCTCCTTC	
261	GGAAGGAG CUGAUGAG X CGAA IGGCGGCG		CGCCGCCC C CTCCTTCC	
262	CGGAAGGA CUGAUGAG X CGAA IGGGCGGC		GCCGCCCC C TCCTTCCG	
263	GCGGAAGG CUGAUGAG X CGAA IGGGGCGG		CCGCCCCC T CCTTCCGC	
265	UGGCGGAA CUGAUGAG X CGAA IAGGGGGC		GCCCCCTC C TTCCGCCA	
266	CUGGCGGA CUGAUGAG X CGAA IGAGGGGG		CCCCCTCC T TCCGCCAG	
269	CACCUGGC CUGAUGAG X CGAA IAAGGAGG		CCTCCTTC C GCCAGGTG	
272	GGACACCU CUGAUGAG X CGAA ICGGAAGG		CCTTCCGC C AGGTGTCC	
273	AGGACACC CUGAUGAG X CGAA IGCGGAAG		CTTCCGCC A GGTGTCCT	
280	UUCAGGCA CUGAUGAG X CGAA IACACCUG		CAGGTGTC C TGCCTGAA	
281	CUUCAGGC CUGAUGAG X CGAA IGACACCU		AGGTGTCC T GCCTGAAG	
284	CUCCUUCA CUGAUGAG X CGAA ICAGGACA		TGTCCTGC C TGAAGGAG	
285	GCUCCUUC CUGAUGAG X CGAA IGCAGGAC		GTCCTGCC T GAAGGAGC	
294	GGGCCACC CUGAUGAG X CGAA ICUCCUUC		GAAGGAGC T GGTGGCCC	
301	AGCACUCG CUGAUGAG X CGAA ICCACCAG		CTGGTGGC C CGAGTGCT	
302	CAGCACUC CUGAUGAG X CGAA IGCCACCA		TGGTGGCC C GAGTGCTG	
309	GCCUCUGC CUGAUGAG X CGAA ICACUCGG		CCGAGTGC T GCAGAGGC	
312	ACAGCCUC CUGAUGAG X CGAA ICAGCACU		AGTGCTGC A GAGGCTGT	
318	GCUCGCAC CUGAUGAG X CGAA ICCUCUGC		GCAGAGGC T GTGCGAGC	
345	CGAAGGCC CUGAUGAG X CGAA ICACGUUC		GAACGTGC T GGCCTTCG	

Table IV

349	AAGCCGAA CUGAUGAG X CGAA ICCAGCAC		GTGCTGGC C TTCGGCTT	
350	GAAGCCGA CUGAUGAG X CGAA IGCCAGCA		TGCTGGCC T TCGGCTTC	
356	CAGCGCGA CUGAUGAG X CGAA ICCGAAGG		CCTTCGGC T TCGCGCTG	
363	CGUCCAGC CUGAUGAG X CGAA ICGCGAAG		CTTCGCGC T GCTGGACG	
366	CCCCGUCC CUGAUGAG X CGAA ICAGCGCG		CGCGCTGC T GGACGGGG	
376	CCCCCGCG CUGAUGAG X CGAA ICCCCGUC		GACGGGGC C CGCGGGGG	
377	GCCCCCGC CUGAUGAG X CGAA IGCCCCGU		ACGGGGCC C GCGGGGGC	
386	CUCGGGGG CUGAUGAG X CGAA ICCCCCGC		GCGGGGGC C CCCCCGAG	
387	CCUCGGGG CUGAUGAG X CGAA IGCCCCCG		CGGGGGCC C CCCCGAGG	
388	GCCUCGGG CUGAUGAG X CGAA IGGCCCCC		GGGGGCCC C CCCGAGGC	
389	GGCCUCGG CUGAUGAG X CGAA IGGGCCCC		GGGGCCCC C CCGAGGCC	
390	AGGCCUCG CUGAUGAG X CGAA IGGGGCCC		GGGCCCCC C CGAGGCCT	
391	AAGGCCUC CUGAUGAG X CGAA IGGGGGCC		GGCCCCCC C GAGGCCTT	
397	GUGGUGAA CUGAUGAG X CGAA ICCUCGGG		CCCGAGGC C TTCACCAC	
398	GGUGGUGA CUGAUGAG X CGAA IGCCUCGG		CCGAGGCC T TCACCACC	
401	GCUGGUGG CUGAUGAG X CGAA IAAGGCCU		AGGCCTTC A CCACCAGC	
403	ACGCUGGU CUGAUGAG X CGAA IUGAAGGC		GCCTTCAC C ACCAGCGT	
404	CACGCUGG CUGAUGAG X CGAA IGUGAAGG		CCTTCACC A CCAGCGTG	
406	CGCACGCU CUGAUGAG X CGAA IUGGUGAA		TTCACCAC C AGCGTGCG	
407	GCGCACGC CUGAUGAG X CGAA IGUGGUGA		TCACCACC A GCGTGCGC	
416	CAGGUAGC CUGAUGAG X CGAA ICGCACGC		GCGTGCGC A GCTACCTG	
419	GGGCAGGU CUGAUGAG X CGAA ICUGCGCA		TGCGCAGC T ACCTGCCC	
422	GUUGGGCA CUGAUGAG X CGAA IUAGCUGC		GCAGCTAC C TGCCCAAC	
423	UGUUGGGC CUGAUGAG X CGAA IGUAGCUG		CAGCTACC T GCCCAACA	
426	CCGUGUUG CUGAUGAG X CGAA ICAGGUAG		CTACCTGC C CAACACGG	
427	ACCGUGUU CUGAUGAG X CGAA IGCAGGUA		TACCTGCC C AACACGGT	
428	CACCGUGU CUGAUGAG X CGAA IGGCAGGU		ACCTGCCC A ACACGGTG	
431	GGUCACCG CUGAUGAG X CGAA IUUGGGCA		TGCCCAAC A CGGTGACC	
439	AGUGCGUC CUGAUGAG X CGAA IUCACCGU		ACGGTGAC C GACGCACT	
445	CCCCGCAG CUGAUGAG X CGAA ICGUCGGU		ACCGACGC A CTGCGGGG	
447	UCCCCCGC CUGAUGAG X CGAA IUGCGUCG		CGACGCAC T GCGGGGGA	
471	GCAGCAGC CUGAUGAG X CGAA ICCCCCAC		GTGGGGGC T GCTGCTGC	
474	GGCGCAGC CUGAUGAG X CGAA ICAGCCCC		GGGGCTGC T GCTGCGCC	
477	CGCGGCGC CUGAUGAG X CGAA ICAGCAGC		GCTGCTGC T GCGCCGCG	
482	GCCCACGC CUGAUGAG X CGAA ICGCAGCA		TGCTGCGC C GCGTGGGC	
501	GGUGAACC CUGAUGAG X CGAA ICACGUCG		CGACGTGC T GGTTCACC	
507	CCAGCAGG CUGAUGAG X CGAA IAACCAGC		GCTGGTTC A CCTGCTGG	
509	UGCCAGCA CUGAUGAG X CGAA IUGAACCA		TGGTTCAC C TGCTGGCA	
510	GUGCCAGC CUGAUGAG X CGAA IGUGAACC		GGTTCACC T GCTGGCAC	
513	AGCGUGCC CUGAUGAG X CGAA ICAGGUGA		TCACCTGC T GGCACGCT	
517	GCGCAGCG CUGAUGAG X CGAA ICCAGCAG		CTGCTGGC A CGCTGCGC	
521	GAGCGCGC CUGAUGAG X CGAA ICGUGCCA		TGGCACGC T GCGCGCTC	
528	GCACAAAG CUGAUGAG X CGAA ICGCGCAG		CTGCGCGC T CTTTGTGC	
530	CAGCACAA CUGAUGAG X CGAA IAGCGCGC		GCGCGCTC T TTGTGCTG	
537	GAGCCACC CUGAUGAG X CGAA ICACAAAG		CTTTGTGC T GGTGGCTC	
544	CAGCUGGG CUGAUGAG X CGAA ICCACCAG		CTGGTGGC T CCCAGCTG	
546	CGCAGCUG CUGAUGAG X CGAA IAGCCACC		GGTGGCTC C CAGCTGCG	

Table IV

547	GCGCAGCU CUGAUGAG X CGAA IGAGCCAC		GTGGCTCC C AGCTGCGC	
548	GGCGCAGC CUGAUGAG X CGAA IGGAGCCA		TGGCTCCC A GCTGCGCC	
551	GUAGGCGC CUGAUGAG X CGAA ICUGGGAG		CTCCCAGC T GCGCCTAC	
556	ACCUGGUA CUGAUGAG X CGAA ICGCAGCU		AGCTGCGC C TACCAGGT	
557	CACCUGGU CUGAUGAG X CGAA IGCGCAGC		GCTGCGCC T ACCAGGTG	
560	GCACACCU CUGAUGAG X CGAA IUAGGCGC		GCGCCTAC C AGGTGTGC	
561	CGCACACC CUGAUGAG X CGAA IGUAGGCG		CGCCTACC A GGTGTGCG	
573	ACAGCGGC CUGAUGAG X CGAA ICCCGCAC		GTGCGGGC C GCCGCTGT	
576	GGUACAGC CUGAUGAG X CGAA ICGGCCCG		CGGGCCGC C GCTGTACC	
579	GCUGGUAC CUGAUGAG X CGAA ICGGCGGC		GCCGCCGC T GTACCAGC	
584	GCCGAGCU CUGAUGAG X CGAA IUACAGCG		CGCTGTAC C AGCTCGGC	
585	CGCCGAGC CUGAUGAG X CGAA IGUACAGC		GCTGTACC A GCTCGGCG	
588	CAGCGCCG CUGAUGAG X CGAA ICUGGUAC		GTACCAGC T CGGCGCTG	
595	UGAGUGGC CUGAUGAG X CGAA ICGCCGAG		CTCGGCGC T GCCACTCA	
598	GCCUGAGU CUGAUGAG X CGAA ICAGCGCC		GGCGCTGC C ACTCAGGC	
599	GGCCUGAG CUGAUGAG X CGAA IGCAGCGC		GCGCTGCC A CTCAGGCC	
601	CGGGCCUG CUGAUGAG X CGAA IUGGCAGC		GCTGCCAC T CAGGCCCG	
603	GCCGGGCC CUGAUGAG X CGAA IAGUGGCA		TGCCACTC A GGCCCGGC	
607	GGGGGCCG CUGAUGAG X CGAA ICCUGAGU		ACTCAGGC C CGGCCCCC	
608	CGGGGGCC CUGAUGAG X CGAA IGCCUGAG		CTCAGGCC C GGCCCCCG	
612	GUGGCGGG CUGAUGAG X CGAA ICCGGGCC		GGCCCGGC C CCCGCCAC	
613	UGUGGCGG CUGAUGAG X CGAA IGCCGGGC		GCCCGGCC C CCGCCACA	
614	GUGUGGCG CUGAUGAG X CGAA IGGCCGGG		CCCGGCCC C CGCCACAC	
615	CGUGUGGC CUGAUGAG X CGAA IGGGCCGG		CCGGCCCC C GCCACACG	
618	UAGCGUGU CUGAUGAG X CGAA ICGGGGGC		GCCCCCGC C ACACGCTA	
619	CUAGCGUG CUGAUGAG X CGAA IGCGGGGG		CCCCCGCC A CACGCTAG	
621	CACUAGCG CUGAUGAG X CGAA IUGGCGGG		CCCGCCAC A CGCTAGTG	
625	GGUCCACU CUGAUGAG X CGAA ICGUGUGG		CCACACGC T AGTGGACC	
633	GCCUUCGG CUGAUGAG X CGAA IUCCACUA		TAGTGGAC C CCGAAGGC	
634	CGCCUUCG CUGAUGAG X CGAA IGUCCACU		AGTGGACC C CGAAGGCG	
635	ACGCCUUC CUGAUGAG X CGAA IGGUCCAC		GTGGACCC C GAAGGCGT	
645	CGCAUCCC CUGAUGAG X CGAA IACGCCUU		AAGGCGTC T GGGATGCG	
661	UGGUUCCA CUGAUGAG X CGAA ICCCGUUC		GAACGGGC C TGGAACCA	
662	AUGGUUCC CUGAUGAG X CGAA IGCCCGUU		AACGGGCC T GGAACCAT	
668	GACGCUAU CUGAUGAG X CGAA IUUCCAGG		CCTGGAAC C ATAGCGTC	
669	UGACGCUA CUGAUGAG X CGAA IGUUCCAG		CTGGAACC A TAGCGTCA	
677	GGCCUCCC CUGAUGAG X CGAA IACGCUAU		ATAGCGTC A GGGAGGCC	
685	GGGACCCC CUGAUGAG X CGAA ICCUCCCU		AGGGAGGC C GGGGTCCC	
692	GCCCAGGG CUGAUGAG X CGAA IACCCCGG		CCGGGGTC C CCCTGGGC	
693	GGCCCAGG CUGAUGAG X CGAA IGACCCCG		CGGGGTCC C CCTGGGCC	
694	AGGCCCAG CUGAUGAG X CGAA IGGACCCC		GGGGTCCC C CTGGGCCT	
695	CAGGCCCA CUGAUGAG X CGAA IGGGACCC		GGGTCCCC C TGGGCCTG	
696	GCAGGCCC CUGAUGAG X CGAA IGGGGACC		GGTCCCCC T GGGCCTGC	
701	GGCUGGCA CUGAUGAG X CGAA ICCCAGGG		CCCTGGGC C TGCCAGCC	
702	GGGCUGGC CUGAUGAG X CGAA IGCCCAGG		CCTGGGCC T GCCAGCCC	
705	CCGGGGCU CUGAUGAG X CGAA ICAGGCCC		GGGCCTGC C AGCCCCGG	
706	CCCGGGGC CUGAUGAG X CGAA IGCAGGCC		GGCCTGCC A GCCCCGGG	

Table IV

709	GCACCCGG CUGAUGAG X CGAA ICUGGCAG		CTGCCAGC C CCGGGTGC	
710	CGCACCCG CUGAUGAG X CGAA IGCUGGCA		TGCCAGCC C CGGGTGCG	
711	UCGCACCC CUGAUGAG X CGAA IGGCUGGC		GCCAGCCC C GGGTGCGA	
734	GCUGGCAC CUGAUGAG X CGAA ICCCCCGC		GCGGGGGC A GTGCCAGC	
739	CUUCGGCU CUGAUGAG X CGAA ICACUGCC		GGCAGTGC C AGCCGAAG	
740	ACUUCGGC CUGAUGAG X CGAA IGCACUGC		GCAGTGCC A GCCGAAGT	
743	CAGACUUC CUGAUGAG X CGAA ICUGGCAC		GTGCCAGC C GAAGTCTG	
750	GCAACGGC CUGAUGAG X CGAA IACUUCGG		CCGAAGTC T GCCGTTGC	
753	UGGGCAAC CUGAUGAG X CGAA ICAGACUU		AAGTCTGC C GTTGCCCA	
759	GCCUCUUG CUGAUGAG X CGAA ICAACGGC		GCCGTTGC C CAAGAGGC	
760	GGCCUCUU CUGAUGAG X CGAA IGCAACGG		CCGTTGCC C AAGAGGCC	
761	GGGCCUCU CUGAUGAG X CGAA IGGCAACG		CGTTGCCC A AGAGGCCC	
768	CACGCCUG CUGAUGAG X CGAA ICCUCUUG		CAAGAGGC C CAGGCGTG	
769	CCACGCCU CUGAUGAG X CGAA IGCCUCUU		AAGAGGCC C AGGCGTGG	
770	GCCACGCC CUGAUGAG X CGAA IGGCCUCU		AGAGGCCC A GGCGTGGC	
781	UCAGGGGC CUGAUGAG X CGAA ICGCCACG		CGTGGCGC T GCCCCTGA	
784	GGCUCAGG CUGAUGAG X CGAA ICAGCGCC		GGCGCTGC C CCTGAGCC	
785	CGGCUCAG CUGAUGAG X CGAA IGCAGCGC		GCGCTGCC C CTGAGCCG	
786	CCGGCUCA CUGAUGAG X CGAA IGGCAGCG		CGCTGCCC C TGAGCCGG	
787	UCCGGCUC CUGAUGAG X CGAA IGGGCAGC		GCTGCCCC T GAGCCGGA	
792	UCCGCUCC CUGAUGAG X CGAA ICUCAGGG		CCCTGAGC C GGAGCGGA	
804	GCCCAACG CUGAUGAG X CGAA ICGUCCGC		GCGGACGC C CGTTGGGC	
805	UGCCCAAC CUGAUGAG X CGAA IGCGUCCG		CGGACGCC C GTTGGGCA	
813	AGGACCCC CUGAUGAG X CGAA ICCCAACG		CGTTGGGC A GGGGTCCT	
820	UGGGCCCA CUGAUGAG X CGAA IACCCCUG		CAGGGGTC C TGGGCCCA	
821	GUGGGCCC CUGAUGAG X CGAA IGACCCCU		AGGGGTCC T GGGCCCAC	
826	CCCGGGUG CUGAUGAG X CGAA ICCCAGGA		TCCTGGGC C CACCCGGG	
827	GCCCGGGU CUGAUGAG X CGAA IGCCCAGG		CCTGGGCC C ACCCGGGC	
828	UGCCCGGG CUGAUGAG X CGAA IGGCCCAG		CTGGGCCC A CCCGGGCA	
830	CCUGCCCG CUGAUGAG X CGAA IUGGGCCC		GGGCCCAC C CGGGCAGG	
831	UCCUGCCC CUGAUGAG X CGAA IGUGGGCC		GGCCCACC C GGGCAGGA	
836	ACGCGUCC CUGAUGAG X CGAA ICCCGGGU		ACCCGGGC A GGACGCGT	
849	GGUCACUC CUGAUGAG X CGAA IUCCACGC		GCGTGGAC C GAGTGACC	
857	GAAACCAC CUGAUGAG X CGAA IUCACUCG		CGAGTGAC C GTGGTTTC	
866	CACCACAC CUGAUGAG X CGAA IAAACCAC		GTGGTTTC T GTGTGGTG	
877	CUGGCAGG CUGAUGAG X CGAA IACACCAC		GTGGTGTC A CCTGCCAG	
879	GUCUGGCA CUGAUGAG X CGAA IUGACACC		GGTGTCAC C TGCCAGAC	
880	GGUCUGGC CUGAUGAG X CGAA IGUGACAC		GTGTCACC T GCCAGACC	
883	GCGGGUCU CUGAUGAG X CGAA ICAGGUGA		TCACCTGC C AGACCCGC	
884	GGCGGGUC CUGAUGAG X CGAA IGCAGGUG		CACCTGCC A GACCCGCC	
888	CUUCGGCG CUGAUGAG X CGAA IUCUGGCA		TGCCAGAC C CGCCGAAG	
889	UCUUCGGC CUGAUGAG X CGAA IGUCUGGC		GCCAGACC C GCCGAAGA	
892	GCUUCUUC CUGAUGAG X CGAA ICGGGUCU		AGACCCGC C GAAGAAGC	
901	AAAGAGGU CUGAUGAG X CGAA ICUUCUUC		GAAGAAGC C ACCTCTTT	
902	CAAAGAGG CUGAUGAG X CGAA IGCUUCUU		AAGAAGCC A CCTCTTTG	
904	UCCAAAGA CUGAUGAG X CGAA IUGGCUUC		GAAGCCAC C TCTTTGGA	
905	CUCCAAAG CUGAUGAG X CGAA IGUGGCUU		AAGCCACC T CTTTGGAG	

Table IV

907	CCCUCCAA CUGAUGAG X CGAA IAGGUGGC		GCCACCTC T TTGGAGGG	
921	UGCCAGAG CUGAUGAG X CGAA ICGCACCC		GGGTGCGC T CTCTGGCA	
923	CGUGCCAG CUGAUGAG X CGAA IAGCGCAC		GTGCGCTC T CTGGCACG	
925	CGCGUGCC CUGAUGAG X CGAA IAGAGCGC		GCGCTCTC T GGCACGCG	
929	GUGGCGCG CUGAUGAG X CGAA ICCAGAGA		TCTCTGGC A CGCGCCAC	
935	GUGGGAGU CUGAUGAG X CGAA ICGCGUGC		GCACGCGC C ACTCCCAC	
936	GGUGGGAG CUGAUGAG X CGAA IGCGCGUG		CACGCGCC A CTCCCACC	
938	UGGGUGGG CUGAUGAG X CGAA IUGGCGCG		CGCGCCAC T CCCACCCA	
940	GAUGGGUG CUGAUGAG X CGAA IAGUGGCG		CGCCACTC C CACCCATC	
941	GGAUGGGU CUGAUGAG X CGAA IGAGUGGC		GCCACTCC C ACCCATCC	
942	CGGAUGGG CUGAUGAG X CGAA IGGAGUGG		CCACTCCC A CCCATCCG	
944	CACGGAUG CUGAUGAG X CGAA IUGGGAGU		ACTCCCAC C CATCCGTG	
945	CCACGGAU CUGAUGAG X CGAA IGUGGGAG		CTCCCACC C ATCCGTGG	
946	CCCACGGA CUGAUGAG X CGAA IGGUGGGA		TCCCACCC A TCCGTGGG	
949	CGGCCCAC CUGAUGAG X CGAA IAUGGGUG		CACCCATC C GTGGGCCG	
956	GUGCUGGC CUGAUGAG X CGAA ICCCACGG		CCGTGGGC C GCCAGCAC	
959	GUGGUGCU CUGAUGAG X CGAA ICGGCCCA		TGGGCCGC C AGCACCAC	
960	CGUGGUGC CUGAUGAG X CGAA IGCGGCCC		GGGCCGCC A GCACCACG	
963	CCGCGUGG CUGAUGAG X CGAA ICUGGCGG		CCGCCAGC A CCACGCGG	
965	GCCCGCGU CUGAUGAG X CGAA IUGCUGGC		GCCAGCAC C ACGCGGGC	
966	GGCCCGCG CUGAUGAG X CGAA IGUGCUGG		CCAGCACC A CGCGGGCC	
974	GGAUGGGG CUGAUGAG X CGAA ICCCGCGU		ACGCGGGC C CCCCATCC	
975	UGGAUGGG CUGAUGAG X CGAA IGCCCGCG		CGCGGGCC C CCCATCCA	
976	GUGGAUGG CUGAUGAG X CGAA IGGCCCGC		GCGGGCCC C CCATCCAC	
977	UGUGGAUG CUGAUGAG X CGAA IGGGCCCG		CGGGCCCC C CATCCACA	
978	AUGUGGAU CUGAUGAG X CGAA IGGGGCCC		GGGCCCCC C ATCCACAT	
979	GAUGUGGA CUGAUGAG X CGAA IGGGGGCC		GGCCCCCC A TCCACATC	
982	CGCGAUGU CUGAUGAG X CGAA IAUGGGGG		CCCCCATC C ACATCGCG	
983	CCGCGAUG CUGAUGAG X CGAA IGAUGGGG		CCCCATCC A CATCGCGG	
985	GGCCGCGA CUGAUGAG X CGAA IUGGAUGG		CCATCCAC A TCGCGGCC	
993	GACGUGGU CUGAUGAG X CGAA ICCGCGAU		ATCGCGGC C ACCACGTC	
994	GGACGUGG CUGAUGAG X CGAA IGCCGCGA		TCGCGGCC A CCACGTCC	
996	AGGGACGU CUGAUGAG X CGAA IUGGCCGC		GCGGCCAC C ACGTCCCT	
997	CAGGGACG CUGAUGAG X CGAA IGUGGCCG		CGGCCACC A CGTCCCTG	
1002	UGUCCCAG CUGAUGAG X CGAA IACGUGGU		ACCACGTC C CTGGGACA	
1003	GUGUCCCA CUGAUGAG X CGAA IGACGUGG		CCACGTCC C TGGGACAC	
1004	CGUGUCCC CUGAUGAG X CGAA IGGACGUG		CACGTCCC T GGGACACG	
1010	ACAAGGCG CUGAUGAG X CGAA IUCCCAGG		CCTGGGAC A CGCCTTGT	
1014	GGGGACAA CUGAUGAG X CGAA ICGUGUCC		GGACACGC C TTGTCCCC	
1015	GGGGGACA CUGAUGAG X CGAA IGCGUGUC		GACACGCC T TGTCCCCC	
1020	ACACCGGG CUGAUGAG X CGAA IACAAGGC		GCCTTGTC C CCCGGTGT	
1021	UACACCGG CUGAUGAG X CGAA IGACAAGG		CCTTGTCC C CCGGTGTA	
1022	GUACACCG CUGAUGAG X CGAA IGGACAAG		CTTGTCCC C CGGTGTAC	
1023	CGUACACC CUGAUGAG X CGAA IGGGACAA		TTGTCCCC C GGTGTACG	
1033	UUGGUCUC CUGAUGAG X CGAA ICGUACAC		GTGTACGC C GAGACCAA	
1039	AAGUGCUU CUGAUGAG X CGAA IUCUCGGC		GCCGAGAC C AAGCACTT	
1040	GAAGUGCU CUGAUGAG X CGAA IGUCUCGG		CCGAGACC A AGCACTTC	

Table IV

1044	AGAGGAAG CUGAUGAG X CGAA ICUUGGUC		GACCAAGC A CTTCCTCT	
1046	GUAGAGGA CUGAUGAG X CGAA IUGCUUGG		CCAAGCAC T TCCTCTAC	
1049	GGAGUAGA CUGAUGAG X CGAA IAAGUGCU		AGCACTTC C TCTACTCC	
1050	AGGAGUAG CUGAUGAG X CGAA IGAAGUGC		GCACTTCC T CTACTCCT	
1052	UGAGGAGU CUGAUGAG X CGAA IAGGAAGU		ACTTCCTC T ACTCCTCA	
1055	GCCUGAGG CUGAUGAG X CGAA IUAGAGGA		TCCTCTAC T CCTCAGGC	
1057	UCGCCUGA CUGAUGAG X CGAA IAGUAGAG		CTCTACTC C TCAGGCGA	
1058	GUCGCCUG CUGAUGAG X CGAA IGAGUAGA		TCTACTCC T CAGGCGAC	
1060	UUGUCGCC CUGAUGAG X CGAA IAGGAGUA		TACTCCTC A GGCGACAA	
1067	CUGCUCCU CUGAUGAG X CGAA IUCGCCUG		CAGGCGAC A AGGAGCAG	
1074	GCCGCAGC CUGAUGAG X CGAA ICUCCUUG		CAAGGAGC A GCTGCGGC	
1077	AGGGCCGC CUGAUGAG X CGAA ICUGCUCC		GGAGCAGC T GCGGCCCT	
1083	GGAAGGAG CUGAUGAG X CGAA ICCGCAGC		GCTGCGGC C CTCCTTCC	
1084	AGGAAGGA CUGAUGAG X CGAA IGCCGCAG		CTGCGGCC C TCCTTCCT	
1085	UAGGAAGG CUGAUGAG X CGAA IGGCCGCA		TGCGGCCC T CCTTCCTA	
1087	AGUAGGAA CUGAUGAG X CGAA IAGGGCCG		CGGCCCTC C TTCCTACT	
1088	GAGUAGGA CUGAUGAG X CGAA IGAGGGCC		GGCCCTCC T TCCTACTC	
1091	GCUGAGUA CUGAUGAG X CGAA IAAGGAGG		CCTCCTTC C TACTCAGC	
1092	AGCUGAGU CUGAUGAG X CGAA IGAAGGAG		CTCCTTCC T ACTCAGCT	
1095	GAGAGCUG CUGAUGAG X CGAA IUAGGAAG		CTTCCTAC T CAGCTCTC	
1097	CAGAGAGC CUGAUGAG X CGAA IAGUAGGA		TCCTACTC A GCTCTCTG	
1100	CCUCAGAG CUGAUGAG X CGAA ICUGAGUA		TACTCAGC T CTCTGAGG	
1102	GGCCUCAG CUGAUGAG X CGAA IAGCUGAG		CTCAGCTC T CTGAGGCC	
1104	UGGGCCUC CUGAUGAG X CGAA IAGAGCUG		CAGCTCTC T GAGGCCCA	
1110	UCAGGCUG CUGAUGAG X CGAA ICCUCAGA		TCTGAGGC C CAGCCTGA	
1111	GUCAGGCU CUGAUGAG X CGAA IGCCUCAG		CTGAGGCC C AGCCTGAC	
1112	AGUCAGGC CUGAUGAG X CGAA IGGCCUCA		TGAGGCCC A GCCTGACT	
1115	GCCAGUCA CUGAUGAG X CGAA ICUGGGCC		GGCCCAGC C TGACTGGC	
1116	CGCCAGUC CUGAUGAG X CGAA IGCUGGGC		GCCCAGCC T GACTGGCG	
1120	CGAGCGCC CUGAUGAG X CGAA IUCAGGCU		AGCCTGAC T GGCGCTCG	
1126	AGCCUCCG CUGAUGAG X CGAA ICGCCAGU		ACTGGCGC T CGGAGGCT	
1134	UCUCCACG CUGAUGAG X CGAA ICCUCCGA		TCGGAGGC T CGTGGAGA	
1144	AGAAAGAU CUGAUGAG X CGAA IUCUCCAC		GTGGAGAC C ATCTTTCT	
1145	CAGAAAGA CUGAUGAG X CGAA IGUCUCCA		TGGAGACC A TCTTTCTG	
1148	ACCCAGAA CUGAUGAG X CGAA IAUGGUCU		AGACCATC T TTCTGGGT	
1152	UGGAACCC CUGAUGAG X CGAA IAAAGAUG		CATCTTTC T GGGTTCCA	
1159	CAGGGCCU CUGAUGAG X CGAA IAACCCAG		CTGGGTTC C AGGCCCTG	
1160	CCAGGGCC CUGAUGAG X CGAA IGAACCCA		TGGGTTCC A GGCCCTGG	
1164	GCAUCCAG CUGAUGAG X CGAA ICCUGGAA		TTCCAGGC C CTGGATGC	
1165	GGCAUCCA CUGAUGAG X CGAA IGCCUGGA		TCCAGGCC C TGGATGCC	
1166	UGGCAUCC CUGAUGAG X CGAA IGGCCUGG		CCAGGCCC T GGATGCCA	
1173	GAGUCCCU CUGAUGAG X CGAA ICAUCCAG		CTGGATGC C AGGGACTC	
1174	GGAGUCCC CUGAUGAG X CGAA IGCAUCCA		TGGATGCC A GGGACTCC	
1180	CUGCGGGG CUGAUGAG X CGAA IUCCCUGG		CCAGGGAC T CCCCGCAG	
1182	ACCUGCGG CUGAUGAG X CGAA IAGUCCCU		AGGGACTC C CCGCAGGT	
1183	AACCUGCG CUGAUGAG X CGAA IGAGUCCC		GGGACTCC C CGCAGGTT	
1184	CAACCUGC CUGAUGAG X CGAA IGGAGUCC		GGACTCCC C GCAGGTTG	

Table IV

1187	GGGCAACC CUGAUGAG X CGAA ICGGGGAG		CTCCCCGC A GGTTGCCC	
1194	GCAGGCGG CUGAUGAG X CGAA ICAACCUG		CAGGTTGC C CCGCCTGC	
1195	GGCAGGCG CUGAUGAG X CGAA IGCAACCU		AGGTTGCC C CGCCTGCC	
1196	GGGCAGGC CUGAUGAG X CGAA IGGCAACC		GGTTGCCC C GCCTGCCC	
1199	CUGGGGCA CUGAUGAG X CGAA ICGGGGCA		TGCCCCGC C TGCCCCAG	
1200	GCUGGGGC CUGAUGAG X CGAA IGCGGGGC		GCCCCGCC T GCCCCAGC	
1203	AGCGCUGG CUGAUGAG X CGAA ICAGGCGG		CCGCCTGC C CCAGCGCT	
1204	UAGCGCUG CUGAUGAG X CGAA IGCAGGCG		CGCCTGCC C CAGCGCTA	
1205	GUAGCGCU CUGAUGAG X CGAA IGGCAGGC		GCCTGCCC C AGCGCTAC	
1206	AGUAGCGC CUGAUGAG X CGAA IGGGCAGG		CCTGCCCC A GCGCTACT	
1211	UUGCCAGU CUGAUGAG X CGAA ICGCUGGG		CCCAGCGC T ACTGGCAA	
1214	CAUUUGCC CUGAUGAG X CGAA IUAGCGCU		AGCGCTAC T GGCAAATG	
1218	GCCGCAUU CUGAUGAG X CGAA ICCAGUAG		CTACTGGC A AATGCGGC	
1227	GAAACAGG CUGAUGAG X CGAA ICCGCAUU		AATGCGGC C CCTGTTTC	
1228	AGAAACAG CUGAUGAG X CGAA IGCCGCAU		ATGCGGCC C CTGTTTCT	
1229	CAGAAACA CUGAUGAG X CGAA IGGCCGCA		TGCGGCCC C TGTTTCTG	
1230	CCAGAAAC CUGAUGAG X CGAA IGGGCCGC		GCGGCCCC T GTTTCTGG	
1236	GCAGCUCC CUGAUGAG X CGAA IAAACAGG		CCTGTTTC T GGAGCTGC	
1242	UCCCAAGC CUGAUGAG X CGAA ICUCCAGA		TCTGGAGC T GCTTGGGA	
1245	GGUUCCCA CUGAUGAG X CGAA ICAGCUCC		GGAGCTGC T TGGGAACC	
1253	CUGCGCGU CUGAUGAG X CGAA IUUCCCAA		TTGGGAAC C ACGCGCAG	
1254	ACUGCGCG CUGAUGAG X CGAA IGUUCCCA		TGGGAACC A CGCGCAGT	
1260	AGGGGCAC CUGAUGAG X CGAA ICGCGUGG		CCACGCGC A GTGCCCCT	
1265	CCCGUAGG CUGAUGAG X CGAA ICACUGCG		CGCAGTGC C CCTACGGG	
1266	CCCCGUAG CUGAUGAG X CGAA IGCACUGC		GCAGTGCC C CTACGGGG	
1267	ACCCCGUA CUGAUGAG X CGAA IGGCACUG		CAGTGCCC C TACGGGGT	
1268	CACCCCGU CUGAUGAG X CGAA IGGGCACU		AGTGCCCC T ACGGGGTG	
1278	UCUUGAGG CUGAUGAG X CGAA ICACCCCG		CGGGGTGC T CCTCAAGA	
1280	CGUCUUGA CUGAUGAG X CGAA IAGCACCC		GGGTGCTC C TCAAGACG	
1281	GCGUCUUG CUGAUGAG X CGAA IGAGCACC		GGTGCTCC T CAAGACGC	
1283	GUGCGUCU CUGAUGAG X CGAA IAGGAGCA		TGCTCCTC A AGACGCAC	
1290	GCGGGCAG CUGAUGAG X CGAA ICGUCUUG		CAAGACGC A CTGCCCGC	
1292	CAGCGGGC CUGAUGAG X CGAA IUGCGUCU		AGACGCAC T GCCCGCTG	
1295	UCGCAGCG CUGAUGAG X CGAA ICAGUGCG		CGCACTGC C CGCTGCGA	
1296	CUCGCAGC CUGAUGAG X CGAA IGCAGUGC		GCACTGCC C GCTGCGAG	
1299	CAGCUCGC CUGAUGAG X CGAA ICGGGCAG		CTGCCCGC T GCGAGCTG	
1306	GUGACCGC CUGAUGAG X CGAA ICUCGCAG		CTGCGAGC T GCGGTCAC	
1313	UGCUGGGG CUGAUGAG X CGAA IACCGCAG		CTGCGGTC A CCCCAGCA	
1315	GCUGCUGG CUGAUGAG X CGAA IUGACCGC		GCGGTCAC C CCAGCAGC	
1316	GGCUGCUG CUGAUGAG X CGAA IGUGACCG		CGGTCACC C CAGCAGCC	
1317	CGGCUGCU CUGAUGAG X CGAA IGGUGACC		GGTCACCC C AGCAGCCG	
1318	CCGGCUGC CUGAUGAG X CGAA IGGGUGAC		GTCACCCC A GCAGCCGG	
1321	ACACCGGC CUGAUGAG X CGAA ICUGGGGU		ACCCCAGC A GCCGGTGT	
1324	CAGACACC CUGAUGAG X CGAA ICUGCUGG		CCAGCAGC C GGTGTCTG	
1331	CCGGGCAC CUGAUGAG X CGAA IACACCGG		CCGGTGTC T GTGCCCGG	
1336	UUCUCCCG CUGAUGAG X CGAA ICACAGAC		GTCTGTGC C CGGGAGAA	
1337	CUUCUCCC CUGAUGAG X CGAA IGCACAGA		TCTGTGCC C GGGAGAAG	

Table IV

1347	AGCCCUGG CUGAUGAG X CGAA ICUUCUCC		GGAGAAGC C CCAGGGCT	
1348	GAGCCCUG CUGAUGAG X CGAA IGCUUCUC		GAGAAGCC C CAGGGCTC	
1349	AGAGCCCU CUGAUGAG X CGAA IGGCUUCU		AGAAGCCC C AGGGCTCT	
1350	CAGAGCCC CUGAUGAG X CGAA IGGGCUUC		GAAGCCCC A GGGCTCTG	
1355	CGCCACAG CUGAUGAG X CGAA ICCCUGGG		CCCAGGGC T CTGTGGCG	
1357	GCCGCCAC CUGAUGAG X CGAA IAGCCCUG		CAGGGCTC T GTGGCGGC	
1366	UCCUCGGG CUGAUGAG X CGAA ICCGCCAC		GTGGCGGC C CCCGAGGA	
1367	CUCCUCGG CUGAUGAG X CGAA IGCCGCCA		TGGCGGCC C CCGAGGAG	
1368	CCUCCUCG CUGAUGAG X CGAA IGGCCGCC		GGCGGCCC C CGAGGAGG	
1369	UCCUCCUC CUGAUGAG X CGAA IGGGCCGC		GCGGCCCC C GAGGAGGA	
1382	GGGGUCUG CUGAUGAG X CGAA IUCCUCCU		AGGAGGAC A CAGACCCC	
1384	CGGGGGUC CUGAUGAG X CGAA IUGUCCUC		GAGGACAC A GACCCCCG	
1388	GCGACGGG CUGAUGAG X CGAA IUCUGUGU		ACACAGAC C CCCGTCGC	
1389	GGCGACGG CUGAUGAG X CGAA IGUCUGUG		CACAGACC C CCGTCGCC	
1390	AGGCGACG CUGAUGAG X CGAA IGGUCUGU		ACAGACCC C CGTCGCCT	
1391	CAGGCGAC CUGAUGAG X CGAA IGGGUCUG		CAGACCCC C GTCGCCTG	
1397	CUGCACCA CUGAUGAG X CGAA ICGACGGG		CCCGTCGC C TGGTGCAG	
1398	GCUGCACC CUGAUGAG X CGAA IGCGACGG		CCGTCGCC T GGTGCAGC	
1404	GGAGCAGC CUGAUGAG X CGAA ICACCAGG		CCTGGTGC A GCTGCTCC	
1407	GGCGGAGC CUGAUGAG X CGAA ICUGCACC		GGTGCAGC T GCTCCGCC	
1410	GCUGGCGG CUGAUGAG X CGAA ICAGCUGC		GCAGCTGC T CCGCCAGC	
1412	GUGCUGGC CUGAUGAG X CGAA IAGCAGCU		AGCTGCTC C GCCAGCAC	
1415	GCUGUGCU CUGAUGAG X CGAA ICGGAGCA		TGCTCCGC C AGCACAGC	
1416	UGCUGUGC CUGAUGAG X CGAA IGCGGAGC		GCTCCGCC A GCACAGCA	
1419	GGCUGCUG CUGAUGAG X CGAA ICUGGCGG		CCGCCAGC A CAGCAGCC	
1421	GGGGCUGC CUGAUGAG X CGAA IUGCUGGC		GCCAGCAC A GCAGCCCC	
1424	CCAGGGGC CUGAUGAG X CGAA ICUGUGCU		AGCACAGC A GCCCCTGG	
1427	CUGCCAGG CUGAUGAG X CGAA ICUGCUGU		ACAGCAGC C CCTGGCAG	
1428	CCUGCCAG CUGAUGAG X CGAA IGCUGCUG		CAGCAGCC C CTGGCAGG	
1429	ACCUGCCA CUGAUGAG X CGAA IGGCUGCU		AGCAGCCC C TGGCAGGT	
1430	CACCUGCC CUGAUGAG X CGAA IGGGCUGC		GCAGCCCC T GGCAGGTG	
1434	CGUACACC CUGAUGAG X CGAA ICCAGGGG		CCCCTGGC A GGTGTACG	
1445	CCGCACGA CUGAUGAG X CGAA ICCGUACA		TGTACGGC T TCGTGCGG	
1456	CGCAGGCA CUGAUGAG X CGAA ICCCGCAC		GTGCGGGC C TGCCTGCG	
1457	GCGCAGGC CUGAUGAG X CGAA IGCCCGCA		TGCGGGCC T GCCTGCGC	
1460	CCGGCGCA CUGAUGAG X CGAA ICAGGCCC		GGGCCTGC C TGCGCCGG	
1461	GCCGGCGC CUGAUGAG X CGAA IGCAGGCC		GGCCTGCC T GCGCCGGC	
1466	CACCAGCC CUGAUGAG X CGAA ICGCAGGC		GCCTGCGC C GGCTGGTG	
1470	GGGGCACC CUGAUGAG X CGAA ICCGGCGC		GCGCCGGC T GGTGCCCC	
1476	GGCCUGGG CUGAUGAG X CGAA ICACCAGC		GCTGGTGC C CCCAGGCC	
1477	AGGCCUGG CUGAUGAG X CGAA IGCACCAG		CTGGTGCC C CCAGGCCT	
1478	GAGGCCUG CUGAUGAG X CGAA IGGCACCA		TGGTGCCC C CAGGCCTC	
1479	AGAGGCCU CUGAUGAG X CGAA IGGGCACC		GGTGCCCC C AGGCCTCT	
1480	CAGAGGCC CUGAUGAG X CGAA IGGGGCAC		GTGCCCCC A GGCCTCTG	
1484	GCCCCAGA CUGAUGAG X CGAA ICCUGGGG		CCCCAGGC C TCTGGGGC	
1485	AGCCCCAG CUGAUGAG X CGAA IGCCUGGG		CCCAGGCC T CTGGGGCT	
1487	GGAGCCCC CUGAUGAG X CGAA IAGGCCUG		CAGGCCTC T GGGGCTCC	

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1493	GUGCCUGG CUGAUGAG X CGAA ICCCCAGA		TCTGGGGC T CCAGGCAC	
1495	UUGUGCCU CUGAUGAG X CGAA IAGCCCCA		TGGGGCTC C AGGCACAA	
1496	GUUGUGCC CUGAUGAG X CGAA IGAGCCCC		GGGGCTCC A GGCACAAC	
1500	GUUCGUUG CUGAUGAG X CGAA ICCUGGAG		CTCCAGGC A CAACGAAC	
1502	GCGUUCGU CUGAUGAG X CGAA IUGCCUGG		CCAGGCAC A ACGAACGC	
1511	GAGGAAGC CUGAUGAG X CGAA ICGUUCGU		ACGAACGC C GCTTCCTC	
1514	CCUGAGGA CUGAUGAG X CGAA ICGGCGUU		AACGCCGC T TCCTCAGG	
1517	GUUCCUGA CUGAUGAG X CGAA IAAGCGGC		GCCGCTTC C TCAGGAAC	
1518	UGUUCCUG CUGAUGAG X CGAA IGAAGCGG		CCGCTTCC T CAGGAACA	
1520	GGUGUUCC CUGAUGAG X CGAA IAGGAAGC		GCTTCCTC A GGAACACC	
1526	CUUCUUGG CUGAUGAG X CGAA IUUCCUGA		TCAGGAAC A CCAAGAAG	
1528	AACUUCUU CUGAUGAG X CGAA IUGUUCCU		AGGAACAC C AAGAAGTT	
1529	GAACUUCU CUGAUGAG X CGAA IGUGUUCC		GGAACACC A AGAAGTTC	
1538	CAGGGAGA CUGAUGAG X CGAA IAACUUCU		AGAAGTTC A TCTCCCTG	
1541	CCCCAGGG CUGAUGAG X CGAA IAUGAACU		AGTTCATC T CCCTGGGG	
1543	UUCCCCAG CUGAUGAG X CGAA IAGAUGAA		TTCATCTC C CTGGGGAA	
1544	CUUCCCCA CUGAUGAG X CGAA IGAGAUGA		TCATCTCC C TGGGGAAG	
1545	GCUUCCCC CUGAUGAG X CGAA IGGAGAUG		CATCTCCC T GGGGAAGC	
1554	GCUUGGCA CUGAUGAG X CGAA ICUUCCCC		GGGGAAGC A TGCCAAGC	
1558	GAGAGCUU CUGAUGAG X CGAA ICAUGCUU		AAGCATGC C AAGCTCTC	
1559	CGAGAGCU CUGAUGAG X CGAA IGCAUGCU		AGCATGCC A AGCTCTCG	
1563	GCAGCGAG CUGAUGAG X CGAA ICUUGGCA		TGCCAAGC T CTCGCTGC	
1565	CUGCAGCG CUGAUGAG X CGAA IAGCUUGG		CCAAGCTC T CGCTGCAG	
1569	GCUCCUGC CUGAUGAG X CGAA ICGAGAGC		GCTCTCGC T GCAGGAGC	
1572	UCAGCUCC CUGAUGAG X CGAA ICAGCGAG		CTCGCTGC A GGAGCTGA	
1578	UCCACGUC CUGAUGAG X CGAA ICUCCUGC		GCAGGAGC T GACGTGGA	
1604	CCAAGCGC CUGAUGAG X CGAA IUCCCGCA		TGCGGGAC T GCGCTTGG	
1609	CGCAGCCA CUGAUGAG X CGAA ICGCAGUC		GACTGCGC T TGGCTGCG	
1614	UCCUGCGC CUGAUGAG X CGAA ICCAAGCG		CGCTTGGC T GCGCAGGA	
1619	UGGGCUCC CUGAUGAG X CGAA ICGCAGCC		GGCTGCGC A GGAGCCCA	
1625	AACCCCUG CUGAUGAG X CGAA ICUCCUGC		GCAGGAGC C CAGGGGTT	
1626	CAACCCCU CUGAUGAG X CGAA IGCUCCUG		CAGGAGCC C AGGGGTTG	
1627	CCAACCCC CUGAUGAG X CGAA IGGCUCCU		AGGAGCCC A GGGGTTGG	
1637	CGGAACAC CUGAUGAG X CGAA ICCAACCC		GGGTTGGC T GTGTTCCG	
1644	CUGCGGCC CUGAUGAG X CGAA IAACACAG		CTGTGTTC C GGCCGCAG	
1648	UGCUCUGC CUGAUGAG X CGAA ICCGGAAC		GTTCCGGC C GCAGAGCA	
1651	CGGUGCUC CUGAUGAG X CGAA ICGGCCGG		CCGGCCGC A GAGCACCG	
1656	GCAGACGG CUGAUGAG X CGAA ICUCUGCG		CGCAGAGC A CCGTCTGC	
1658	ACGCAGAC CUGAUGAG X CGAA IUGCUCUG		CAGAGCAC C GTCTGCGT	
1662	CCUCACGC CUGAUGAG X CGAA IACGGUGC		GCACCGTC T GCGTGAGG	
1676	CUUGGCCA CUGAUGAG X CGAA IAUCUCCU		AGGAGATC C TGGCCAAG	
1677	ACUUGGCC CUGAUGAG X CGAA IGAUCUCC		GGAGATCC T GGCCAAGT	
1681	AGGAACUU CUGAUGAG X CGAA ICCAGGAU		ATCCTGGC C AAGTTCCT	
1682	CAGGAACU CUGAUGAG X CGAA IGCCAGGA		TCCTGGCC A AGTTCCTG	
1688	CCAGUGCA CUGAUGAG X CGAA IAACUUGG		CCAAGTTC C TGCACTGG	
1689	GCCAGUGC CUGAUGAG X CGAA IGAACUUG		CAAGTTCC T GCACTGGC	
1692	UCAGCCAG CUGAUGAG X CGAA ICAGGAAC		GTTCCTGC A CTGGCTGA	

Table IV

1694	CAUCAGCC CUGAUGAG X CGAA IUGCAGGA		TCCTGCAC T GGCTGATG	
1698	CACUCAUC CUGAUGAG X CGAA ICCAGUGC		GCACTGGC T GATGAGTG	
1722	ACCUGAGC CUGAUGAG X CGAA ICUCGACG		CGTCGAGC T GCTCAGGT	
1725	AAGACCUG CUGAUGAG X CGAA ICAGCUCG		CGAGCTGC T CAGGTCTT	
1727	GAAAGACC CUGAUGAG X CGAA IAGCAGCU		AGCTGCTC A GGTCTTTC	
1732	UAAAAGAA CUGAUGAG X CGAA IACCUGAG		CTCAGGTC T TTCTTTTA	
1736	GACAUAAA CUGAUGAG X CGAA IAAAGACC		GGTCTTTC T TTTATGTC	
1745	GGUCUCCG CUGAUGAG X CGAA IACAUAAA		TTTATGTC A CGGAGACC	
1753	UGAAACGU CUGAUGAG X CGAA IUCUCCGU		ACGGAGAC C ACGTTTCA	
1754	UUGAAACG CUGAUGAG X CGAA IGUCUCCG		CGGAGACC A CGTTTCAA	
1761	UGUUCUUU CUGAUGAG X CGAA IAAACGUG		CACGTTTC A AAAGAACA	
1769	AAAGAGCC CUGAUGAG X CGAA IUUCUUUU		AAAAGAAC A GGCTCTTT	
1773	AGAAAAAG CUGAUGAG X CGAA ICCUGUUC		GAACAGGC T CTTTTTCT	
1775	GUAGAAAA CUGAUGAG X CGAA IAGCCUGU		ACAGGCTC T TTTTCTAC	
1781	CUUCCGGU CUGAUGAG X CGAA IAAAAAGA		TCTTTTTC T ACCGGAAG	
1784	ACUCUUCC CUGAUGAG X CGAA IUAGAAAA		TTTTCTAC C GGAAGAGT	
1796	CUUGCUCC CUGAUGAG X CGAA IACACUCU		AGAGTGTC T GGAGCAAG	
1802	UUGCAACU CUGAUGAG X CGAA ICUCCAGA		TCTGGAGC A AGTTGCAA	
1809	CAAUGCUU CUGAUGAG X CGAA ICAACUUG		CAAGTTGC A AAGCATTG	
1814	GAUUCCAA CUGAUGAG X CGAA ICUUUGCA		TGCAAAGC A TTGGAATC	
1823	GUGCUGUC CUGAUGAG X CGAA IAUUCCAA		TTGGAATC A GACAGCAC	
1827	UCAAGUGC CUGAUGAG X CGAA IUCUGAUU		AATCAGAC A GCACTTGA	
1830	UCUUCAAG CUGAUGAG X CGAA ICUGUCUG		CAGACAGC A CTTGAAGA	
1832	CCUCUUCA CUGAUGAG X CGAA IUGCUGUC		GACAGCAC T TGAAGAGG	
1845	CCCGCAGC CUGAUGAG X CGAA ICACCCUC		GAGGGTGC A GCTGCGGG	
1848	GCUCCCGC CUGAUGAG X CGAA ICUGCACC		GGTGCAGC T GCGGGAGC	
1857	CUUCCGAC CUGAUGAG X CGAA ICUCCCGC		GCGGGAGC T GTCGGAAG	
1867	CUGACCUC CUGAUGAG X CGAA ICUUCCGA		TCGGAAGC A GAGGTCAG	
1874	AUGCUGCC CUGAUGAG X CGAA IACCUCUG		CAGAGGTC A GGCAGCAT	
1878	CCCGAUGC CUGAUGAG X CGAA ICCUGACC		GGTCAGGC A GCATCGGG	
1881	CUUCCCGA CUGAUGAG X CGAA ICUGCCUG		CAGGCAGC A TCGGGAAG	
1891	GCGGGCCU CUGAUGAG X CGAA ICUUCCCG		CGGGAAGC C AGGCCCGC	
1892	GGCGGGCC CUGAUGAG X CGAA IGCUUCCC		GGGAAGCC A GGCCCGCC	
1896	GCAGGGCG CUGAUGAG X CGAA ICCUGGCU		AGCCAGGC C CGCCCTGC	
1897	AGCAGGGC CUGAUGAG X CGAA IGCCUGGC		GCCAGGCC C GCCCTGCT	
1900	GUCAGCAG CUGAUGAG X CGAA ICGGGCCU		AGGCCCGC C CTGCTGAC	
1901	CGUCAGCA CUGAUGAG X CGAA IGCGGGCC		GGCCCGCC C TGCTGACG	
1902	ACGUCAGC CUGAUGAG X CGAA IGGCGGGC		GCCCGCCC T GCTGACGT	
1905	UGGACGUC CUGAUGAG X CGAA ICAGGGCG		CGCCCTGC T GACGTCCA	
1912	CGGAGUCU CUGAUGAG X CGAA IACGUCAG		CTGACGTC C AGACTCCG	
1913	GCGGAGUC CUGAUGAG X CGAA IGACGUCA		TGACGTCC A GACTCCGC	
1917	UGAAGCGG CUGAUGAG X CGAA IUCUGGAC		GTCCAGAC T CCGCTTCA	
1919	GAUGAAGC CUGAUGAG X CGAA IAGUCUGG		CCAGACTC C GCTTCATC	
1922	GGGGAUGA CUGAUGAG X CGAA ICGGAGUC		GACTCCGC T TCATCCCC	
1925	CUUGGGGA CUGAUGAG X CGAA IAAGCGGA		TCCGCTTC A TCCCCAAG	
1928	AGGCUUGG CUGAUGAG X CGAA IAUGAAGC		GCTTCATC C CCAAGCCT	
1929	CAGGCUUG CUGAUGAG X CGAA IGAUGAAG		CTTCATCC C CAAGCCTG	

Table IV

1930	UCAGGCUU CUGAUGAG X CGAA IGGAUGAA		TTCATCCC C AAGCCTGA	
1931	GUCAGGCU CUGAUGAG X CGAA IGGGAUGA		TCATCCCC A AGCCTGAC	
1935	GCCCGUCA CUGAUGAG X CGAA ICUUGGGG		CCCCAAGC C TGACGGGC	
1936	AGCCCGUC CUGAUGAG X CGAA IGCUUGGG		CCCAAGCC T GACGGGCT	
1944	UCGGCCGC CUGAUGAG X CGAA ICCCGUCA		TGACGGGC T GCGGCCGA	
1950	UCACAAUC CUGAUGAG X CGAA ICCGCAGC		GCTGCGGC C GATTGTGA	
1961	GUAGUCCA CUGAUGAG X CGAA IUUCACAA		TTGTGAAC A TGGACTAC	
1967	CACGACGU CUGAUGAG X CGAA IUCCAUGU		ACATGGAC T ACGTCGTG	
1981	AACGUUCU CUGAUGAG X CGAA ICUCCCAC		GTGGGAGC C AGAACGTT	
1982	GAACGUUC CUGAUGAG X CGAA IGCUCCCA		TGGGAGCC A GAACGTTC	
1991	UUCUCUGC CUGAUGAG X CGAA IAACGUUC		GAACGTTC C GCAGAGAA	
1994	CUUUUCUC CUGAUGAG X CGAA ICGGAACG		CGTTCCGC A GAGAAAAG	
2008	AGACGCUC CUGAUGAG X CGAA ICCCUCUU		AAGAGGGC C GAGCGTCT	
2016	UCGAGGUG CUGAUGAG X CGAA IACGCUCG		CGAGCGTC T CACCTCGA	
2018	CCUCGAGG CUGAUGAG X CGAA IAGACGCU		AGCGTCTC A CCTCGAGG	
2020	ACCCUCGA CUGAUGAG X CGAA IUGAGACG		CGTCTCAC C TCGAGGGT	
2021	CACCCUCG CUGAUGAG X CGAA IGUGAGAC		GTCTCACC T CGAGGGTG	
2035	CUGAACAG CUGAUGAG X CGAA ICCUUCAC		GTGAAGGC A CTGTTCAG	
2037	CGCUGAAC CUGAUGAG X CGAA IUGCCUUC		GAAGGCAC T GTTCAGCG	
2042	GAGCACGC CUGAUGAG X CGAA IAACAGUG		CACTGTTC A GCGTGCTC	
2049	CGUAGUUG CUGAUGAG X CGAA ICACGCUG		CAGCGTGC T CAACTACG	
2051	CUCGUAGU CUGAUGAG X CGAA IAGCACGC		GCGTGCTC A ACTACGAG	
2054	CCGCUCGU CUGAUGAG X CGAA IUUGAGCA		TGCTCAAC T ACGAGCGG	
2072	GAGGCCGG CUGAUGAG X CGAA ICGCCGCG		CGCGGCGC C CCGGCCTC	
2073	GGAGGCCG CUGAUGAG X CGAA IGCGCCGC		GCGGCGCC C CGGCCTCC	
2074	AGGAGGCC CUGAUGAG X CGAA IGGCGCCG		CGGCGCCC C GGCCTCCT	
2078	GCCCAGGA CUGAUGAG X CGAA ICCGGGGC		GCCCCGGC C TCCTGGGC	
2079	CGCCCAGG CUGAUGAG X CGAA IGCCGGGG		CCCCGGCC T CCTGGGCG	
2081	GGCGCCCA CUGAUGAG X CGAA IAGGCCGG		CCGGCCTC C TGGGCGCC	
2082	AGGCGCCC CUGAUGAG X CGAA IGAGGCCG		CGGCCTCC T GGGCGCCT	
2089	AGCACAGA CUGAUGAG X CGAA ICGCCCAG		CTGGGCGC C TCTGTGCT	
2090	CAGCACAG CUGAUGAG X CGAA IGCGCCCA		TGGGCGCC T CTGTGCTG	
2092	CCCAGCAC CUGAUGAG X CGAA IAGGCGCC		GGCGCCTC T GTGCTGGG	
2097	CCAGGCCC CUGAUGAG X CGAA ICACAGAG		CTCTGTGC T GGGCCTGG	
2102	AUCGUCCA CUGAUGAG X CGAA ICCCAGCA		TGCTGGGC C TGGACGAT	
2103	UAUCGUCC CUGAUGAG X CGAA IGCCCAGC		GCTGGGCC T GGACGATA	
2114	GGCCCUGU CUGAUGAG X CGAA IAUAUCGU		ACGATATC C ACAGGGCC	
2115	AGGCCCUG CUGAUGAG X CGAA IGAUAUCG		CGATATCC A CAGGGCCT	
2117	CCAGGCCC CUGAUGAG X CGAA IUGGAUAU		ATATCCAC A GGGCCTGG	
2122	GUGCGCCA CUGAUGAG X CGAA ICCCUGUG		CACAGGGC C TGGCGCAC	
2123	GGUGCGCC CUGAUGAG X CGAA IGCCCUGU		ACAGGGCC T GGCGCACC	
2129	CACGAAGG CUGAUGAG X CGAA ICGCCAGG		CCTGGCGC A CCTTCGTG	
2131	AGCACGAA CUGAUGAG X CGAA IUGCGCCA		TGGCGCAC C TTCGTGCT	
2132	CAGCACGA CUGAUGAG X CGAA IGUGCGCC		GGCGCACC T TCGTGCTG	
2139	GCACACGC CUGAUGAG X CGAA ICACGAAG		CTTCGTGC T GCGTGTGC	
2152	GGGUCCUG CUGAUGAG X CGAA ICCCGCAC		GTGCGGGC C CAGGACCC	
2153	CGGGUCCU CUGAUGAG X CGAA IGCCCGCA		TGCGGGCC C AGGACCCG	

Table IV

2154	GCGGGUCC CUGAUGAG X CGAA IGGCCCGC		GCGGGCCC A GGACCCGC	
2159	AGGCGGCG CUGAUGAG X CGAA IUCCUGGG		CCCAGGAC C CGCCGCCT	
2160	CAGGCGGC CUGAUGAG X CGAA IGUCCUGG		CCAGGACC C GCCGCCTG	
2163	GCUCAGGC CUGAUGAG X CGAA ICGGGUCC		GGACCCGC C GCCTGAGC	
2166	ACAGCUCA CUGAUGAG X CGAA ICGGCGGG		CCCGCCGC C TGAGCTGT	
2167	UACAGCUC CUGAUGAG X CGAA IGCGGCGG		CCGCCGCC T GAGCTGTA	
2172	CAAAGUAC CUGAUGAG X CGAA ICUCAGGC		GCCTGAGC T GTACTTTG	
2177	CUUGACAA CUGAUGAG X CGAA IUACAGCU		AGCTGTAC T TTGTCAAG	
2183	AUCCACCU CUGAUGAG X CGAA IACAAAGU		ACTTTGTC A AGGTGGAT	
2210	GGGGAUGG CUGAUGAG X CGAA IUCGUACG		CGTACGAC A CCATCCCC	
2212	UGGGGGAU CUGAUGAG X CGAA IUGUCGUA		TACGACAC C ATCCCCCA	
2213	CUGGGGGA CUGAUGAG X CGAA IGUGUCGU		ACGACACC A TCCCCCAG	
2216	GUCCUGGG CUGAUGAG X CGAA IAUGGUGU		ACACCATC C CCCAGGAC	
2217	UGUCCUGG CUGAUGAG X CGAA IGAUGGUG		CACCATCC C CCAGGACA	
2218	CUGUCCUG CUGAUGAG X CGAA IGGAUGGU		ACCATCCC C CAGGACAG	
2219	CCUGUCCU CUGAUGAG X CGAA IGGGAUGG		CCATCCCC C AGGACAGG	
2220	GCCUGUCC CUGAUGAG X CGAA IGGGGAUG		CATCCCCC A GGACAGGC	
2225	CGUGAGCC CUGAUGAG X CGAA IUCCUGGG		CCCAGGAC A GGCTCACG	
2229	CCUCCGUG CUGAUGAG X CGAA ICCUGUCC		GGACAGGC T CACGGAGG	
2231	GACCUCCG CUGAUGAG X CGAA IAGCCUGU		ACAGGCTC A CGGAGGTC	
2240	GCUGGCGA CUGAUGAG X CGAA IACCUCCG		CGGAGGTC A TCGCCAGC	
2245	AUGAUGCU CUGAUGAG X CGAA ICGAUGAC		GTCATCGC C AGCATCAT	
2246	GAUGAUGC CUGAUGAG X CGAA IGCGAUGA		TCATCGCC A GCATCATC	
2249	UUUGAUGA CUGAUGAG X CGAA ICUGGCGA		TCGCCAGC A TCATCAAA	
2252	GGGUUUGA CUGAUGAG X CGAA IAUGCUGG		CCAGCATC A TCAAACCC	
2255	CUGGGGUU CUGAUGAG X CGAA IAUGAUGC		GCATCATC A AACCCCAG	
2259	UGUUCUGG CUGAUGAG X CGAA IUUUGAUG		CATCAAAC C CCAGAACA	
2260	GUGUUCUG CUGAUGAG X CGAA IGUUUGAU		ATCAAACC C CAGAACAC	
2261	CGUGUUCU CUGAUGAG X CGAA IGGUUUGA		TCAAACCC C AGAACACG	
2262	ACGUGUUC CUGAUGAG X CGAA IGGGUUUG		CAAACCCC A GAACACGT	
2267	GCAGUACG CUGAUGAG X CGAA IUUCUGGG		CCCAGAAC A CGTACTGC	
2273	ACGCACGC CUGAUGAG X CGAA IUACGUGU		ACACGTAC T GCGTGCGT	
2290	UGGACCAC CUGAUGAG X CGAA ICAUACCG		CGGTATGC C GTGGTCCA	
2297	GGCCUUCU CUGAUGAG X CGAA IACCACGG		CCGTGGTC C AGAAGGCC	
2298	CGGCCUUC CUGAUGAG X CGAA IGACCACG		CGTGGTCC A GAAGGCCG	
2305	CCAUGGGC CUGAUGAG X CGAA ICCUUCUG		CAGAAGGC C GCCCATGG	
2308	UGCCCAUG CUGAUGAG X CGAA ICGGCCUU		AAGGCCGC C CATGGGCA	
2309	GUGCCCAU CUGAUGAG X CGAA IGCGGCCU		AGGCCGCC C ATGGGCAC	
2310	CGUGCCCA CUGAUGAG X CGAA IGGCGGCC		GGCCGCCC A TGGGCACG	
2316	UGCGGACG CUGAUGAG X CGAA ICCCAUGG		CCATGGGC A CGTCCGCA	
2321	GGCCUUGC CUGAUGAG X CGAA IACGUGCC		GGCACGTC C GCAAGGCC	
2324	GAAGGCCU CUGAUGAG X CGAA ICGGACGU		ACGTCCGC A AGGCCTTC	
2329	CUCUUGAA CUGAUGAG X CGAA ICCUUGCG		CGCAAGGC C TTCAAGAG	
2330	GCUCUUGA CUGAUGAG X CGAA IGCCUUGC		GCAAGGCC T TCAAGAGC	
2333	GUGGCUCU CUGAUGAG X CGAA IAAGGCCU		AGGCCTTC A AGAGCCAC	
2339	AGAGACGU CUGAUGAG X CGAA ICUCUUGA		TCAAGAGC C ACGTCTCT	
2340	UAGAGACG CUGAUGAG X CGAA IGCUCUUG		CAAGAGCC A CGTCTCTA	

Table IV

2345	CAAGGUAG CUGAUGAG X CGAA IACGUGGC		GCCACGTC T CTACCTTG	
2347	GUCAAGGU CUGAUGAG X CGAA IAGACGUG		CACGTCTC T ACCTTGAC	
2350	UCUGUCAA CUGAUGAG X CGAA IUAGAGAC		GTCTCTAC C TTGACAGA	
2351	GUCUGUCA CUGAUGAG X CGAA IGUAGAGA		TCTCTACC T TGACAGAC	
2356	UGGAGGUC CUGAUGAG X CGAA IUCAAGGU		ACCTTGAC A GACCTCCA	
2360	CGGCUGGA CUGAUGAG X CGAA IUCUGUCA		TGACAGAC C TCCAGCCG	
2361	ACGGCUGG CUGAUGAG X CGAA IGUCUGUC		GACAGACC T CCAGCCGT	
2363	GUACGGCU CUGAUGAG X CGAA IAGGUCUG		CAGACCTC C AGCCGTAC	
2364	UGUACGGC CUGAUGAG X CGAA IGAGGUCU		AGACCTCC A GCCGTACA	
2367	GCAUGUAC CUGAUGAG X CGAA ICUGGAGG		CCTCCAGC C GTACATGC	
2372	CUGUCGCA CUGAUGAG X CGAA IUACGGCU		AGCCGTAC A TGCGACAG	
2379	CCACGAAC CUGAUGAG X CGAA IUCGCAUG		CATGCGAC A GTTCGTGG	
2389	UGCAGGUG CUGAUGAG X CGAA ICCACGAA		TTCGTGGC T CACCTGCA	
2391	CCUGCAGG CUGAUGAG X CGAA IAGCCACG		CGTGGCTC A CCTGCAGG	
2393	CUCCUGCA CUGAUGAG X CGAA IUGAGCCA		TGGCTCAC C TGCAGGAG	
2394	UCUCCUGC CUGAUGAG X CGAA IGUGAGCC		GGCTCACC T GCAGGAGA	
2397	UGGUCUCC CUGAUGAG X CGAA ICAGGUGA		TCACCTGC A GGAGACCA	
2404	AGCGGGCU CUGAUGAG X CGAA IUCUCCUG		CAGGAGAC C AGCCCGCT	
2405	CAGCGGGC CUGAUGAG X CGAA IGUCUCCU		AGGAGACC A GCCCGCTG	
2408	CCUCAGCG CUGAUGAG X CGAA ICUGGUCU		AGACCAGC C CGCTGAGG	
2409	CCCUCAGC CUGAUGAG X CGAA IGCUGGUC		GACCAGCC C GCTGAGGG	
2412	CAUCCCUC CUGAUGAG X CGAA ICGGGCUG		CAGCCCGC T GAGGGATG	
2422	AUGACGAC CUGAUGAG X CGAA ICAUCCCU		AGGGATGC C GTCGTCAT	
2429	CUGCUCGA CUGAUGAG X CGAA IACGACGG		CCGTCGTC A TCGAGCAG	
2436	AGGAGCUC CUGAUGAG X CGAA ICUCGAUG		CATCGAGC A GAGCTCCT	
2441	CAGGGAGG CUGAUGAG X CGAA ICUCUGCU		AGCAGAGC T CCTCCCTG	
2443	UUCAGGGA CUGAUGAG X CGAA IAGCUCUG		CAGAGCTC C TCCCTGAA	
2444	AUUCAGGG CUGAUGAG X CGAA IGAGCUCU		AGAGCTCC T CCCTGAAT	
2446	UCAUUCAG CUGAUGAG X CGAA IAGGAGCU		AGCTCCTC C CTGAATGA	
2447	CUCAUUCA CUGAUGAG X CGAA IGAGGAGC		GCTCCTCC C TGAATGAG	
2448	CCUCAUUC CUGAUGAG X CGAA IGGAGGAG		CTCCTCCC T GAATGAGG	
2458	CCACUGCU CUGAUGAG X CGAA ICCUCAUU		AATGAGGC C AGCAGTGG	
2459	GCCACUGC CUGAUGAG X CGAA IGCCUCAU		ATGAGGCC A GCAGTGGC	
2462	GAGGCCAC CUGAUGAG X CGAA ICUGGCCU		AGGCCAGC A GTGGCCTC	
2468	GUCGAAGA CUGAUGAG X CGAA ICCACUGC		GCAGTGGC C TCTTCGAC	
2469	CGUCGAAG CUGAUGAG X CGAA IGCCACUG		CAGTGGCC T CTTCGACG	
2471	GACGUCGA CUGAUGAG X CGAA IAGGCCAC		GTGGCCTC T TCGACGTC	
2480	GCGUAGGA CUGAUGAG X CGAA IACGUCGA		TCGACGTC T TCCTACGC	
2483	GAAGCGUA CUGAUGAG X CGAA IAAGACGU		ACGTCTTC C TACGCTTC	
2484	UGAAGCGU CUGAUGAG X CGAA IGAAGACG		CGTCTTCC T ACGCTTCA	
2489	GCACAUGA CUGAUGAG X CGAA ICGUAGGA		TCCTACGC T TCATGTGC	
2492	GUGGCACA CUGAUGAG X CGAA IAAGCGUA		TACGCTTC A TGTGCCAC	
2498	GGCGUGGU CUGAUGAG X CGAA ICACAUGA		TCATGTGC C ACCACGCC	
2499	CGGCGUGG CUGAUGAG X CGAA IGCACAUG		CATGTGCC A CCACGCCG	
2501	CACGGCGU CUGAUGAG X CGAA IUGGCACA		TGTGCCAC C ACGCCGTG	
2502	GCACGGCG CUGAUGAG X CGAA IGUGGCAC		GTGCCACC A CGCCGTGC	
2506	AUGCGCAC CUGAUGAG X CGAA ICGUGGUG		CACCACGC C GTGCGCAT	

Table IV

2513	GCCCCUGA CUGAUGAG X CGAA ICGCACGG		CCGTGCGC A TCAGGGGC	
2516	CUUGCCCC CUGAUGAG X CGAA IAUGCGCA		TGCGCATC A GGGGCAAG	
2522	GUAGGACU CUGAUGAG X CGAA ICCCCUGA		TCAGGGGC A AGTCCTAC	
2527	UGGACGUA CUGAUGAG X CGAA IACUUGCC		GGCAAGTC C TACGTCCA	
2528	CUGGACGU CUGAUGAG X CGAA IGACUUGC		GCAAGTCC T ACGTCCAG	
2534	CUGGCACU CUGAUGAG X CGAA IACGUAGG		CCTACGTC C AGTGCCAG	
2535	CCUGGCAC CUGAUGAG X CGAA IGACGUAG		CTACGTCC A GTGCCAGG	
2540	GAUCCCCU CUGAUGAG X CGAA ICACUGGA		TCCAGTGC C AGGGGATC	
2541	GGAUCCCC CUGAUGAG X CGAA IGCACUGG		CCAGTGCC A GGGGATCC	
2549	GCCCUGCG CUGAUGAG X CGAA IAUCCCCU		AGGGGATC C CGCAGGGC	
2550	AGCCCUGC CUGAUGAG X CGAA IGAUCCCC		GGGGATCC C GCAGGGCT	
2553	UGGAGCCC CUGAUGAG X CGAA ICGGGAUC		GATCCCGC A GGGCTCCA	
2558	GAGGAUGG CUGAUGAG X CGAA ICCCUGCG		CGCAGGGC T CCATCCTC	
2560	GAGAGGAU CUGAUGAG X CGAA IAGCCCUG		CAGGGCTC C ATCCTCTC	
2561	GGAGAGGA CUGAUGAG X CGAA IGAGCCCU		AGGGCTCC A TCCTCTCC	
2564	CGUGGAGA CUGAUGAG X CGAA IAUGGAGC		GCTCCATC C TCTCCACG	
2565	GCGUGGAG CUGAUGAG X CGAA IGAUGGAG		CTCCATCC T CTCCACGC	
2567	CAGCGUGG CUGAUGAG X CGAA IAGGAUGG		CCATCCTC T CCACGCTG	
2569	AGCAGCGU CUGAUGAG X CGAA IAGAGGAU		ATCCTCTC C ACGCTGCT	
2570	GAGCAGCG CUGAUGAG X CGAA IGAGAGGA		TCCTCTCC A CGCTGCTC	
2574	UGCAGAGC CUGAUGAG X CGAA ICGUGGAG		CTCCACGC T GCTCTGCA	
2577	GGCUGCAG CUGAUGAG X CGAA ICAGCGUG		CACGCTGC T CTGCAGCC	
2579	CAGGCUGC CUGAUGAG X CGAA IAGCAGCG		CGCTGCTC T GCAGCCTG	
2582	GCACAGGC CUGAUGAG X CGAA ICAGAGCA		TGCTCTGC A GCCTGTGC	
2585	GUAGCACA CUGAUGAG X CGAA ICUGCAGA		TCTGCAGC C TGTGCTAC	
2586	CGUAGCAC CUGAUGAG X CGAA IGCUGCAG		CTGCAGCC T GTGCTACG	
2591	GUCGCCGU CUGAUGAG X CGAA ICACAGGC		GCCTGTGC T ACGGCGAC	
2600	GUUCUCCA CUGAUGAG X CGAA IUCGCCGU		ACGGCGAC A TGGAGAAC	
2609	AAACAGCU CUGAUGAG X CGAA IUUCUCCA		TGGAGAAC A AGCTGTTT	
2613	CCGCAAAC CUGAUGAG X CGAA ICUUGUUC		GAACAAGC T GTTTGCGG	
2640	GCAGGAGC CUGAUGAG X CGAA ICCCGUCC		GGACGGGC T GCTCCTGC	
2643	AACGCAGG CUGAUGAG X CGAA ICAGCCCG		CGGGCTGC T CCTGCGTT	
2645	CAAACGCA CUGAUGAG X CGAA IAGCAGCC		GGCTGCTC C TGCGTTTG	
2646	CCAAACGC CUGAUGAG X CGAA IGAGCAGC		GCTGCTCC T GCGTTTGG	
2666	CACCAACA CUGAUGAG X CGAA IAAAUCAU		ATGATTTC T TGTTGGTG	
2677	AGGUGAGG CUGAUGAG X CGAA IUCACCAA		TTGGTGAC A CCTCACCT	
2679	UGAGGUGA CUGAUGAG X CGAA IUGUCACC		GGTGACAC C TCACCTCA	
2680	GUGAGGUG CUGAUGAG X CGAA IGUGUCAC		GTGACACC T CACCTCAC	
2682	GGGUGAGG CUGAUGAG X CGAA IAGGUGUC		GACACCTC A CCTCACCC	
2684	GUGGGUGA CUGAUGAG X CGAA IUGAGGUG		CACCTCAC C TCACCCAC	
2685	CGUGGGUG CUGAUGAG X CGAA IGUGAGGU		ACCTCACC T CACCCACG	
2687	CGCGUGGG CUGAUGAG X CGAA IAGGUGAG		CTCACCTC A CCCACGCG	
2689	UUCGCGUG CUGAUGAG X CGAA IUGAGGUG		CACCTCAC C CACGCGAA	
2690	UUUCGCGU CUGAUGAG X CGAA IGUGAGGU		ACCTCACC C ACGCGAAA	
2691	UUUUCGCG CUGAUGAG X CGAA IGGUGAGG		CCTCACCC A CGCGAAAA	
2701	CUGAGGAA CUGAUGAG X CGAA IUUUUCGC		GCGAAAAC C TTCCTCAG	
2702	CCUGAGGA CUGAUGAG X CGAA IGUUUUCG		CGAAAACC T TCCTCAGG	

Table IV

2705	GGUCCUGA CUGAUGAG X CGAA IAAGGUUU		AAACCTTC C TCAGGACC	
2706	GGGUCCUG CUGAUGAG X CGAA IGAAGGUU		AACCTTCC T CAGGACCC	
2708	CAGGGUCC CUGAUGAG X CGAA IAGGAAGG		CCTTCCTC A GGACCCTG	
2713	CGGACCAG CUGAUGAG X CGAA IUCCUGAG		CTCAGGAC C CTGGTCCG	
2714	UCGGACCA CUGAUGAG X CGAA IGUCCUGA		TCAGGACC C TGGTCCGA	
2715	CUCGGACC CUGAUGAG X CGAA IGGUCCUG		CAGGACCC T GGTCCGAG	
2720	GACACCUC CUGAUGAG X CGAA IACCAGGG		CCCTGGTC C GAGGTGTC	
2729	AUACUCAG CUGAUGAG X CGAA IACACCUC		GAGGTGTC C CTGAGTAT	
2730	CAUACUCA CUGAUGAG X CGAA IGACACCU		AGGTGTCC C TGAGTATG	
2731	CCAUACUC CUGAUGAG X CGAA IGGACACC		GGTGTCCC T GAGTATGG	
2741	CACCACGC CUGAUGAG X CGAA ICCAUACU		AGTATGGC T GCGTGGTG	
2753	CUUCCGCA CUGAUGAG X CGAA IUUCACCA		TGGTGAAC T TGCGGAAG	
2764	UUCACCAC CUGAUGAG X CGAA IUCUUCCG		CGGAAGAC A GTGGTGAA	
2774	UACAGGGA CUGAUGAG X CGAA IUUCACCA		TGGTGAAC T TCCCTGTA	
2777	UUCUACAG CUGAUGAG X CGAA IAAGUUCA		TGAACTTC C CTGTAGAA	
2778	CUUCUACA CUGAUGAG X CGAA IGAAGUUC		GAACTTCC C TGTAGAAG	
2779	UCUUCUAC CUGAUGAG X CGAA IGGAAGUU		AACTTCCC T GTAGAAGA	
2794	CCACCCAG CUGAUGAG X CGAA ICCUCGUC		GACGAGGC C CTGGGTGG	
2795	GCCACCCA CUGAUGAG X CGAA IGCCUCGU		ACGAGGCC C TGGGTGGC	
2796	UGCCACCC CUGAUGAG X CGAA IGGCCUCG		CGAGGCCC T GGGTGGCA	
2804	AAAAGCCG CUGAUGAG X CGAA ICCACCCA		TGGGTGGC A CGGCTTTT	
2809	UGAACAAA CUGAUGAG X CGAA ICCGUGCC		GGCACGGC T TTTGTTCA	
2817	CCGGCAUC CUGAUGAG X CGAA IAACAAAA		TTTTGTTC A GATGCCGG	
2823	CGUGGGCC CUGAUGAG X CGAA ICAUCUGA		TCAGATGC C GGCCCACG	
2827	AGGCCGUG CUGAUGAG X CGAA ICCGGCAU		ATGCCGGC C CACGGCCT	
2828	UAGGCCGU CUGAUGAG X CGAA IGCCGGCA		TGCCGGCC C ACGGCCTA	
2829	AUAGGCCG CUGAUGAG X CGAA IGGCCGGC		GCCGGCCC A CGGCCTAT	
2834	GGGGAAUA CUGAUGAG X CGAA ICCGUGGG		CCCACGGC C TATTCCCC	
2835	AGGGGAAU CUGAUGAG X CGAA IGCCGUGG		CCACGGCC T ATTCCCCT	
2840	GCACCAGG CUGAUGAG X CGAA IAAUAGGC		GCCTATTC C CCTGGTGC	
2841	CGCACCAG CUGAUGAG X CGAA IGAAUAGG		CCTATTCC C CTGGTGCG	
2842	CCGCACCA CUGAUGAG X CGAA IGGAAUAG		CTATTCCC C TGGTGCGG	
2843	GCCGCACC CUGAUGAG X CGAA IGGGAAUA		TATTCCCC T GGTGCGGC	
2852	CAGCAGCA CUGAUGAG X CGAA ICCGCACC		GGTGCGGC C TGCTGCTG	
2853	CCAGCAGC CUGAUGAG X CGAA IGCCGCAC		GTGCGGCC T GCTGCTGG	
2856	UAUCCAGC CUGAUGAG X CGAA ICAGGCCG		CGGCCTGC T GCTGGATA	
2859	GGGUAUCC CUGAUGAG X CGAA ICAGCAGG		CCTGCTGC T GGATACCC	
2866	AGGGUCCG CUGAUGAG X CGAA IUAUCCAG		CTGGATAC C CGGACCCT	
2867	CAGGGUCC CUGAUGAG X CGAA IGUAUCCA		TGGATACC C GGACCCTG	
2872	ACCUCCAG CUGAUGAG X CGAA IUCCGGGU		ACCCGGAC C CTGGAGGT	
2873	CACCUCCA CUGAUGAG X CGAA IGUCCGGG		CCCGGACC C TGGAGGTG	
2874	GCACCUCC CUGAUGAG X CGAA IGGUCCGG		CCGGACCC T GGAGGTGC	
2883	AGUCGCUC CUGAUGAG X CGAA ICACCUCC		GGAGGTGC A GAGCGACT	
2891	GCUGGAGU CUGAUGAG X CGAA IUCGCUCU		AGAGCGAC T ACTCCAGC	
2894	AUAGCUGG CUGAUGAG X CGAA IUAGUCGC		GCGACTAC T CCAGCTAT	
2896	GCAUAGCU CUGAUGAG X CGAA IAGUAGUC		GACTACTC C AGCTATGC	
2897	GGCAUAGC CUGAUGAG X CGAA IGAGUAGU		ACTACTCC A GCTATGCC	

Table IV

2900	CCGGGCAU CUGAUGAG X CGAA ICUGGAGU		ACTCCAGC T ATGCCCGG	
2905	GAGGUCCG CUGAUGAG X CGAA ICAUAGCU		AGCTATGC C CGGACCTC	
2906	GGAGGUCC CUGAUGAG X CGAA IGCAUAGC		GCTATGCC C GGACCTCC	
2911	CUGAUGGA CUGAUGAG X CGAA IUCCGGGC		GCCCGGAC C TCCATCAG	
2912	UCUGAUGG CUGAUGAG X CGAA IGUCCGGG		CCCGGACC T CCATCAGA	
2914	GCUCUGAU CUGAUGAG X CGAA IAGGUCCG		CGGACCTC C ATCAGAGC	
2915	GGCUCUGA CUGAUGAG X CGAA IGAGGUCC		GGACCTCC A TCAGAGCC	
2918	ACUGGCUC CUGAUGAG X CGAA IAUGGAGG		CCTCCATC A GAGCCAGT	
2923	GUGAGACU CUGAUGAG X CGAA ICUCUGAU		ATCAGAGC C AGTCTCAC	
2924	GGUGAGAC CUGAUGAG X CGAA IGCUCUGA		TCAGAGCC A GTCTCACC	
2928	UGAAGGUG CUGAUGAG X CGAA IACUGGCU		AGCCAGTC T CACCTTCA	
2930	GUUGAAGG CUGAUGAG X CGAA IAGACUGG		CCAGTCTC A CCTTCAAC	
2932	CGGUUGAA CUGAUGAG X CGAA IUGAGACU		AGTCTCAC C TTCAACCG	
2933	GCGGUUGA CUGAUGAG X CGAA IGUGAGAC		GTCTCACC T TCAACCGC	
2936	GCCGCGGU CUGAUGAG X CGAA IAAGGUGA		TCACCTTC A ACCGCGGC	
2939	GAAGCCGC CUGAUGAG X CGAA IUUGAAGG		CCTTCAAC C GCGGCTTC	
2945	AGCCUUGA CUGAUGAG X CGAA ICCGCGGU		ACCGCGGC T TCAAGGCT	
2948	CCCAGCCU CUGAUGAG X CGAA IAAGCCGC		GCGGCTTC A AGGCTGGG	
2953	UUCCUCCC CUGAUGAG X CGAA ICCUUGAA		TTCAAGGC T GGGAGGAA	
2963	GCGACGCA CUGAUGAG X CGAA IUUCCUCC		GGAGGAAC A TGCGTCGC	
2972	AAAGAGUU CUGAUGAG X CGAA ICGACGCA		TGCGTCGC A AACTCTTT	
2976	CCCCAAAG CUGAUGAG X CGAA IUUUGCGA		TCGCAAAC T CTTTGGGG	
2978	GACCCCAA CUGAUGAG X CGAA IAGUUUGC		GCAAACTC T TTGGGGTC	
2987	CAGCCGCA CUGAUGAG X CGAA IACCCCAA		TTGGGGTC T TGCGGCTG	
2994	GACACUUC CUGAUGAG X CGAA ICCGCAAG		CTTGCGGC T GAAGTGTC	
3003	ACAGGCUG CUGAUGAG X CGAA IACACUUC		GAAGTGTC A CAGCCTGT	
3005	AAACAGGC CUGAUGAG X CGAA IUGACACU		AGTGTCAC A GCCTGTTT	
3008	CAGAAACA CUGAUGAG X CGAA ICUGUGAC		GTCACAGC C TGTTTCTG	
3009	CCAGAAAC CUGAUGAG X CGAA IGCUGUGA		TCACAGCC T GTTTCTGG	
3015	GCAAAUCC CUGAUGAG X CGAA IAAACAGG		CCTGTTTC T GGATTTGC	
3024	UGUUCACC CUGAUGAG X CGAA ICAAAUCC		GGATTTGC A GGTGAACA	
3032	CUGGAGGC CUGAUGAG X CGAA IUUCACCU		AGGTGAAC A GCCTCCAG	
3035	CGUCUGGA CUGAUGAG X CGAA ICUGUUCA		TGAACAGC C TCCAGACG	
3036	CCGUCUGG CUGAUGAG X CGAA IGCUGUUC		GAACAGCC T CCAGACGG	
3038	CACCGUCU CUGAUGAG X CGAA IAGGCUGU		ACAGCCTC C AGACGGTG	
3039	ACACCGUC CUGAUGAG X CGAA IGAGGCUG		CAGCCTCC A GACGGTGT	
3050	GAUGUUGG CUGAUGAG X CGAA ICACACCG		CGGTGTGC A CCAACATC	
3052	UAGAUGUU CUGAUGAG X CGAA IUGCACAC		GTGTGCAC C AACATCTA	
3053	GUAGAUGU CUGAUGAG X CGAA IGUGCACA		TGTGCACC A ACATCTAC	
3056	CUUGUAGA CUGAUGAG X CGAA IUUGGUGC		GCACCAAC A TCTACAAG	
3059	GAUCUUGU CUGAUGAG X CGAA IAUGUUGG		CCAACATC T ACAAGATC	
3062	GAGGAUCU CUGAUGAG X CGAA IUAGAUGU		ACATCTAC A AGATCCTC	
3068	CAGCAGGA CUGAUGAG X CGAA IAUCUUGU		ACAAGATC C TCCTGCTG	
3069	GCAGCAGG CUGAUGAG X CGAA IGAUCUUG		CAAGATCC T CCTGCTGC	
3071	CUGCAGCA CUGAUGAG X CGAA IAGGAUCU		AGATCCTC C TGCTGCAG	
3072	CCUGCAGC CUGAUGAG X CGAA IGAGGAUC		GATCCTCC T GCTGCAGG	
3075	ACGCCUGC CUGAUGAG X CGAA ICAGGAGG		CCTCCTGC T GCAGGCGT	

Table IV

3078	UGUACGCC CUGAUGAG X CGAA ICAGCAGG		CCTGCTGC A GGCGTACA	
3086	GUGAAACC CUGAUGAG X CGAA IUACGCCU		AGGCGTAC A GGTTTCAC	
3093	CACAUGCG CUGAUGAG X CGAA IAAACCUG		CAGGTTTC A CGCATGTG	
3097	AGCACACA CUGAUGAG X CGAA ICGUGAAA		TTTCACGC A TGTGTGCT	
3105	GGAGCUGC CUGAUGAG X CGAA ICACACAU		ATGTGTGC T GCAGCTCC	
3108	AUGGGAGC CUGAUGAG X CGAA ICAGCACA		TGTGCTGC A GCTCCCAT	
3111	GAAAUGGG CUGAUGAG X CGAA ICUGCAGC		GCTGCAGC T CCCATTTC	
3113	AUGAAAUG CUGAUGAG X CGAA IAGCUGCA		TGCAGCTC C CATTTCAT	
3114	GAUGAAAU CUGAUGAG X CGAA IGAGCUGC		GCAGCTCC C ATTTCATC	
3115	UGAUGAAA CUGAUGAG X CGAA IGGAGCUG		CAGCTCCC A TTTCATCA	
3120	CUUGCUGA CUGAUGAG X CGAA IAAAUGGG		CCCATTTC A TCAGCAAG	
3123	AAACUUGC CUGAUGAG X CGAA IAUGAAAU		ATTTCATC A GCAAGTTT	
3126	UCCAAACU CUGAUGAG X CGAA ICUGAUGA		TCATCAGC A AGTTTGGA	
3140	AAAUGUGG CUGAUGAG X CGAA IUUCUUCC		GGAAGAAC C CCACATTT	
3141	AAAAUGUG CUGAUGAG X CGAA IGUUCUUC		GAAGAACC C CACATTTT	
3142	AAAAAUGU CUGAUGAG X CGAA IGGUUCUU		AAGAACCC C ACATTTTT	
3143	GAAAAAUG CUGAUGAG X CGAA IGGGUUCU		AGAACCCC A CATTTTTC	
3145	AGGAAAAA CUGAUGAG X CGAA IUGGGGUU		AACCCCAC A TTTTTCCT	
3152	GACGCGCA CUGAUGAG X CGAA IAAAAAUG		CATTTTTC C TGCGCGTC	
3153	UGACGCGC CUGAUGAG X CGAA IGAAAAAU		ATTTTTCC T GCGCGTCA	
3161	GUCAGAGA CUGAUGAG X CGAA IACGCGCA		TGCGCGTC A TCTCTGAC	
3164	CGUGUCAG CUGAUGAG X CGAA IAUGACGC		GCGTCATC T CTGACACG	
3166	GCCGUGUC CUGAUGAG X CGAA IAGAUGAC		GTCATCTC T GACACGGC	
3170	GGAGGCCG CUGAUGAG X CGAA IUCAGAGA		TCTCTGAC A CGGCCTCC	
3175	CAGAGGGA CUGAUGAG X CGAA ICCGUGUC		GACACGGC C TCCCTCTG	
3176	GCAGAGGG CUGAUGAG X CGAA IGCCGUGU		ACACGGCC T CCCTCTGC	
3178	UAGCAGAG CUGAUGAG X CGAA IAGGCCGU		ACGGCCTC C CTCTGCTA	
3179	GUAGCAGA CUGAUGAG X CGAA IGAGGCCG		CGGCCTCC C TCTGCTAC	
3180	AGUAGCAG CUGAUGAG X CGAA IGGAGGCC		GGCCTCCC T CTGCTACT	
3182	GGAGUAGC CUGAUGAG X CGAA IAGGGAGG		CCTCCCTC T GCTACTCC	
3185	GAUGGAGU CUGAUGAG X CGAA ICAGAGGG		CCCTCTGC T ACTCCATC	
3188	CAGGAUGG CUGAUGAG X CGAA IUAGCAGA		TCTGCTAC T CCATCCTG	
3190	UUCAGGAU CUGAUGAG X CGAA IAGUAGCA		TGCTACTC C ATCCTGAA	
3191	UUUCAGGA CUGAUGAG X CGAA IGAGUAGC		GCTACTCC A TCCTGAAA	
3194	GGCUUUCA CUGAUGAG X CGAA IAUGGAGU		ACTCCATC C TGAAAGCC	
3195	UGGCUUUC CUGAUGAG X CGAA IGAUGGAG		CTCCATCC T GAAAGCCA	
3202	GCGUUCUU CUGAUGAG X CGAA ICUUUCAG		CTGAAAGC C AAGAACGC	
3203	UGCGUUCU CUGAUGAG X CGAA IGCUUUCA		TGAAAGCC A AGAACGCA	
3211	GACAUCCC CUGAUGAG X CGAA ICGUUCUU		AAGAACGC A GGGATGTC	
3222	UGGCCCCC CUGAUGAG X CGAA ICGACAUC		GATGTCGC T GGGGGCCA	
3229	GCGCCCUU CUGAUGAG X CGAA ICCCCCAG		CTGGGGGC C AAGGGCGC	
3230	GGCGCCCU CUGAUGAG X CGAA IGCCCCCA		TGGGGGCC A AGGGCGCC	
3238	GGGCCGGC CUGAUGAG X CGAA ICGCCCUU		AAGGGCGC C GCCGGCCC	
3241	AGAGGGCC CUGAUGAG X CGAA ICGGCGCC		GGCGCCGC C GGCCCTCT	
3245	GGGCAGAG CUGAUGAG X CGAA ICCGGCGG		CCGCCGGC C CTCTGCCC	
3246	AGGGCAGA CUGAUGAG X CGAA IGCCGGCG		CGCCGGCC C TCTGCCCT	
3247	GAGGGCAG CUGAUGAG X CGAA IGGCCGGC		GCCGGCCC T CTGCCCTC	

Table IV

3249	CGGAGGGC CUGAUGAG X CGAA IAGGGCCG		CGGCCCTC T GCCCTCCG	
3252	CCUCGGAG CUGAUGAG X CGAA ICAGAGGG		CCCTCTGC C CTCCGAGG	
3253	GCCUCGGA CUGAUGAG X CGAA IGCAGAGG		CCTCTGCC C TCCGAGGC	
3254	GGCCUCGG CUGAUGAG X CGAA IGGCAGAG		CTCTGCCC T CCGAGGCC	
3256	ACGGCCUC CUGAUGAG X CGAA IAGGGCAG		CTGCCCTC C GAGGCCGT	
3262	CACUGCAC CUGAUGAG X CGAA ICCUCGGA		TCCGAGGC C GTGCAGTG	
3267	ACAGCCAC CUGAUGAG X CGAA ICACGGCC		GGCCGTGC A GTGGCTGT	
3273	GGUGGCAC CUGAUGAG X CGAA ICCACUGC		GCAGTGGC T GTGCCACC	
3278	UGCUUGGU CUGAUGAG X CGAA ICACAGCC		GGCTGTGC C ACCAAGCA	
3279	AUGCUUGG CUGAUGAG X CGAA IGCACAGC		GCTGTGCC A CCAAGCAT	
3281	GAAUGCUU CUGAUGAG X CGAA IUGGCACA		TGTGCCAC C AAGCATTC	
3282	GGAAUGCU CUGAUGAG X CGAA IGUGGCAC		GTGCCACC A AGCATTCC	
3286	AGCAGGAA CUGAUGAG X CGAA ICUUGGUG		CACCAAGC A TTCCTGCT	
3290	CUUGAGCA CUGAUGAG X CGAA IAAUGCUU		AAGCATTC C TGCTCAAG	
3291	GCUUGAGC CUGAUGAG X CGAA IGAAUGCU		AGCATTCC T GCTCAAGC	
3294	UCAGCUUG CUGAUGAG X CGAA ICAGGAAU		ATTCCTGC T CAAGCTGA	
3296	AGUCAGCU CUGAUGAG X CGAA IAGCAGGA		TCCTGCTC A AGCTGACT	
3300	GUCGAGUC CUGAUGAG X CGAA ICUUGAGC		GCTCAAGC T GACTCGAC	
3304	CGGUGUCG CUGAUGAG X CGAA IUCAGCUU		AAGCTGAC T CGACACCG	
3309	UGACACGG CUGAUGAG X CGAA IUCGAGUC		GACTCGAC A CCGTGTCA	
3311	GGUGACAC CUGAUGAG X CGAA IUGUCGAG		CTCGACAC C GTGTCACC	
3317	CACGUAGG CUGAUGAG X CGAA IACACGGU		ACCGTGTC A CCTACGTG	
3319	GGCACGUA CUGAUGAG X CGAA IUGACACG		CGTGTCAC C TACGTGCC	
3320	UGGCACGU CUGAUGAG X CGAA IGUGACAC		GTGTCACC T ACGTGCCA	
3327	CCAGGAGU CUGAUGAG X CGAA ICACGUAG		CTACGTGC C ACTCCTGG	
3328	CCCAGGAG CUGAUGAG X CGAA IGCACGUA		TACGTGCC A CTCCTGGG	
3330	ACCCCAGG CUGAUGAG X CGAA IUGGCACG		CGTGCCAC T CCTGGGGT	
3332	UGACCCCA CUGAUGAG X CGAA IAGUGGCA		TGCCACTC C TGGGGTCA	
3333	GUGACCCC CUGAUGAG X CGAA IGAGUGGC		GCCACTCC T GGGGTCAC	
3340	GUCCUGAG CUGAUGAG X CGAA IACCCCAG		CTGGGGTC A CTCAGGAC	
3342	CUGUCCUG CUGAUGAG X CGAA IUGACCCC		GGGGTCAC T CAGGACAG	
3344	GGCUGUCC CUGAUGAG X CGAA IAGUGACC		GGTCACTC A GGACAGCC	
3349	GUCUGGGC CUGAUGAG X CGAA IUCCUGAG		CTCAGGAC A GCCCAGAC	
3352	UGCGUCUG CUGAUGAG X CGAA ICUGUCCU		AGGACAGC C CAGACGCA	
3353	CUGCGUCU CUGAUGAG X CGAA IGCUGUCC		GGACAGCC C AGACGCAG	
3354	GCUGCGUC CUGAUGAG X CGAA IGGCUGUC		GACAGCCC A GACGCAGC	
3360	GACUCAGC CUGAUGAG X CGAA ICGUCUGG		CCAGACGC A GCTGAGTC	
3363	UCCGACUC CUGAUGAG X CGAA ICUGCGUC		GACGCAGC T GAGTCGGA	
3375	UCCCCGGG CUGAUGAG X CGAA ICUUCCGA		TCGGAAGC T CCCGGGGA	
3377	CGUCCCCG CUGAUGAG X CGAA IAGCUUCC		GGAAGCTC C CGGGGACG	
3378	UCGUCCCC CUGAUGAG X CGAA IGAGCUUC		GAAGCTCC C GGGGACGA	
3390	GGGCAGUC CUGAUGAG X CGAA ICGUCGUC		GACGACGC T GACTGCCC	
3394	UCCAGGGC CUGAUGAG X CGAA IUCAGCGU		ACGCTGAC T GCCCTGGA	
3397	GCCUCCAG CUGAUGAG X CGAA ICAGUCAG		CTGACTGC C CTGGAGGC	
3398	GGCCUCCA CUGAUGAG X CGAA IGCAGUCA		TGACTGCC C TGGAGGCC	
3399	CGGCCUCC CUGAUGAG X CGAA IGGCAGUC		GACTGCCC T GGAGGCCG	
3406	UUGGCUGC CUGAUGAG X CGAA ICCUCCAG		CTGGAGGC C GCAGCCAA	

Table IV

3409	GGGUUGGC CUGAUGAG X CGAA ICGGCCUC		GAGGCCGC A GCCAACCC	
3412	GCCGGGUU CUGAUGAG X CGAA ICUGCGGC		GCCGCAGC C AACCCGGC	
3413	UGCCGGGU CUGAUGAG X CGAA IGCUGCGG		CCGCAGCC A ACCCGGCA	
3416	CAGUGCCG CUGAUGAG X CGAA IUUGGCUG		CAGCCAAC C CGGCACTG	
3417	GCAGUGCC CUGAUGAG X CGAA IGUUGGCU		AGCCAACC C GGCACTGC	
3421	GAGGGCAG CUGAUGAG X CGAA ICCGGGUU		AACCCGGC A CTGCCCTC	
3423	CUGAGGGC CUGAUGAG X CGAA IUGCCGGG		CCCGGCAC T GCCCTCAG	
3426	AGUCUGAG CUGAUGAG X CGAA ICAGUGCC		GGCACTGC C CTCAGACT	
3427	AAGUCUGA CUGAUGAG X CGAA IGCAGUGC		GCACTGCC C TCAGACTT	
3428	GAAGUCUG CUGAUGAG X CGAA IGGCAGUG		CACTGCCC T CAGACTTC	
3430	UUGAAGUC CUGAUGAG X CGAA IAGGGCAG		CTGCCCTC A GACTTCAA	
3434	GGUCUUGA CUGAUGAG X CGAA IUCUGAGG		CCTCAGAC T TCAAGACC	
3437	GAUGGUCU CUGAUGAG X CGAA IAAGUCUG		CAGACTTC A AGACCATC	
3442	UCCAGGAU CUGAUGAG X CGAA IUCUUGAA		TTCAAGAC C ATCCTGGA	
3443	GUCCAGGA CUGAUGAG X CGAA IGUCUUGA		TCAAGACC A TCCTGGAC	
3446	UCAGUCCA CUGAUGAG X CGAA IAUGGUCU		AGACCATC C TGGACTGA	
3447	AUCAGUCC CUGAUGAG X CGAA IGAUGGUC		GACCATCC T GGACTGAT	
3452	UGGCCAUC CUGAUGAG X CGAA IUCCAGGA		TCCTGGAC T GATGGCCA	
3459	GGGCGGGU CUGAUGAG X CGAA ICCAUCAG		CTGATGGC C ACCCGCCC	
3460	UGGGCGGG CUGAUGAG X CGAA IGCCAUCA		TGATGGCC A CCCGCCCA	
3462	UGUGGGCG CUGAUGAG X CGAA IUGGCCAU		ATGGCCAC C CGCCCACA	
3463	CUGUGGGC CUGAUGAG X CGAA IGUGGCCA		TGGCCACC C GCCCACAG	
3466	UGGCUGUG CUGAUGAG X CGAA ICGGGUGG		CCACCCGC C CACAGCCA	
3467	CUGGCUGU CUGAUGAG X CGAA IGCGGGUG		CACCCGCC C ACAGCCAG	
3468	CCUGGCUG CUGAUGAG X CGAA IGGCGGGU		ACCCGCCC A CAGCCAGG	
3470	GGCCUGGC CUGAUGAG X CGAA IUGGGCGG		CCGCCCAC A GCCAGGCC	
3473	CUCGGCCU CUGAUGAG X CGAA ICUGUGGG		CCCACAGC C AGGCCGAG	
3474	UCUCGGCC CUGAUGAG X CGAA IGCUGUGG		CCACAGCC A GGCCGAGA	
3478	CUGCUCUC CUGAUGAG X CGAA ICCUGGCU		AGCCAGGC C GAGAGCAG	
3485	CUGGUGUC CUGAUGAG X CGAA ICUCUCGG		CCGAGAGC A GACACCAG	
3489	GCUGCUGG CUGAUGAG X CGAA IUCUGCUC		GAGCAGAC A CCAGCAGC	
3491	GGGCUGCU CUGAUGAG X CGAA IUGUCUGC		GCAGACAC C AGCAGCCC	
3492	AGGGCUGC CUGAUGAG X CGAA IGUGUCUG		CAGACACC A GCAGCCCT	
3495	GACAGGGC CUGAUGAG X CGAA ICUGGUGU		ACACCAGC A GCCCTGTC	
3498	CGUGACAG CUGAUGAG X CGAA ICUGCUGG		CCAGCAGC C CTGTCACG	
3499	GCGUGACA CUGAUGAG X CGAA IGCUGCUG		CAGCAGCC C TGTCACGC	
3500	GGCGUGAC CUGAUGAG X CGAA IGGCUGCU		AGCAGCCC T GTCACGCC	
3504	GCCCGGCG CUGAUGAG X CGAA IACAGGGC		GCCCTGTC A CGCCGGGC	
3508	UAGAGCCC CUGAUGAG X CGAA ICGUGACA		TGTCACGC C GGGCTCTA	
3513	GGACGUAG CUGAUGAG X CGAA ICCCGGCG		CGCCGGGC T CTACGTCC	
3515	UGGGACGU CUGAUGAG X CGAA IAGCCCGG		CCGGGCTC T ACGTCCCA	
3521	CCUCCCUG CUGAUGAG X CGAA IACGUAGA		TCTACGTC C CAGGGAGG	
3522	CCCUCCCU CUGAUGAG X CGAA IGACGUAG		CTACGTCC C AGGGAGGG	
3523	UCCCUCCC CUGAUGAG X CGAA IGGACGUA		TACGTCCC A GGGAGGGA	
3540	UGGGUGUG CUGAUGAG X CGAA ICCGCCCC		GGGGCGGC C CACACCCA	
3541	CUGGGUGU CUGAUGAG X CGAA IGCCGCCC		GGGCGGCC C ACACCCAG	
3542	CCUGGGUG CUGAUGAG X CGAA IGGCCGCC		GGCGGCCC A CACCCAGG	

Table IV

3544	GGCCUGGG CUGAUGAG X CGAA IUGGGCCG		CGGCCCAC A CCCAGGCC	
3546	CGGGCCUG CUGAUGAG X CGAA IUGUGGGC		GCCCACAC C CAGGCCCG	
3547	GCGGGCCU CUGAUGAG X CGAA IGUGUGGG		CCCACACC C AGGCCCGC	
3548	UGCGGGCC CUGAUGAG X CGAA IGGUGUGG		CCACACCC A GGCCCGCA	
3552	GCGGUGCG CUGAUGAG X CGAA ICCUGGGU		ACCCAGGC C CGCACCGC	
3553	AGCGGUGC CUGAUGAG X CGAA IGCCUGGG		CCCAGGCC C GCACCGCT	
3556	CCCAGCGG CUGAUGAG X CGAA ICGGGCCU		AGGCCCGC A CCGCTGGG	
3558	CUCCCAGC CUGAUGAG X CGAA IUGCGGGC		GCCCGCAC C GCTGGGAG	
3561	AGACUCCC CUGAUGAG X CGAA ICGGUGCG		CGCACCGC T GGGAGTCT	
3569	CAGGCCUC CUGAUGAG X CGAA IACUCCCA		TGGGAGTC T GAGGCCTG	
3575	CUCACUCA CUGAUGAG X CGAA ICCUCAGA		TCTGAGGC C TGAGTGAG	
3576	ACUCACUC CUGAUGAG X CGAA IGCCUCAG		CTGAGGCC T GAGTGAGT	
3592	CAGGCCUC CUGAUGAG X CGAA ICCAAACA		TGTTTGGC C GAGGCCTG	
3598	GACAUGCA CUGAUGAG X CGAA ICCUCGGC		GCCGAGGC C TGCATGTC	
3599	GGACAUGC CUGAUGAG X CGAA IGCCUCGG		CCGAGGCC T GCATGTCC	
3602	GCCGGACA CUGAUGAG X CGAA ICAGGCCU		AGGCCTGC A TGTCCGGC	
3607	CUUCAGCC CUGAUGAG X CGAA IACAUGCA		TGCATGTC C GGCTGAAG	
3611	CAGCCUUC CUGAUGAG X CGAA ICCGGACA		TGTCCGGC T GAAGGCTG	
3618	GGACACUC CUGAUGAG X CGAA ICCUUCAG		CTGAAGGC T GAGTGTCC	
3626	CCUCAGCC CUGAUGAG X CGAA IACACUCA		TGAGTGTC C GGCTGAGG	
3630	CAGGCCUC CUGAUGAG X CGAA ICCGGACA		TGTCCGGC T GAGGCCTG	
3636	CUCGCUCA CUGAUGAG X CGAA ICCUCAGC		GCTGAGGC C TGAGCGAG	
3637	ACUCGCUC CUGAUGAG X CGAA IGCCUCAG		CTGAGGCC T GAGCGAGT	
3649	CCUUGGCU CUGAUGAG X CGAA IACACUCG		CGAGTGTC C AGCCAAGG	
3650	CCCUUGGC CUGAUGAG X CGAA IGACACUC		GAGTGTCC A GCCAAGGG	
3653	CAGCCCUU CUGAUGAG X CGAA ICUGGACA		TGTCCAGC C AAGGGCTG	
3654	UCAGCCCU CUGAUGAG X CGAA IGCUGGAC		GTCCAGCC A AGGGCTGA	
3660	GGACACUC CUGAUGAG X CGAA ICCCUUGG		CCAAGGGC T GAGTGTCC	
3668	GGUGUGCU CUGAUGAG X CGAA IACACUCA		TGAGTGTC C AGCACACC	
3669	AGGUGUGC CUGAUGAG X CGAA IGACACUC		GAGTGTCC A GCACACCT	
3672	GGCAGGUG CUGAUGAG X CGAA ICUGGACA		TGTCCAGC A CACCTGCC	
3674	ACGGCAGG CUGAUGAG X CGAA IUGCUGGA		TCCAGCAC A CCTGCCGT	
3676	AGACGGCA CUGAUGAG X CGAA IUGUGCUG		CAGCACAC C TGCCGTCT	
3677	AAGACGGC CUGAUGAG X CGAA IGUGUGCU		AGCACACC T GCCGTCTT	
3680	GUGAAGAC CUGAUGAG X CGAA ICAGGUGU		ACACCTGC C GTCTTCAC	
3684	GGAAGUGA CUGAUGAG X CGAA IACGGCAG		CTGCCGTC T TCACTTCC	
3687	UGGGGAAG CUGAUGAG X CGAA IAAGACGG		CCGTCTTC A CTTCCCCA	
3689	UGUGGGGA CUGAUGAG X CGAA IUGAAGAC		GTCTTCAC T TCCCCACA	
3692	GCCUGUGG CUGAUGAG X CGAA IAAGUGAA		TTCACTTC C CCACAGGC	
3693	AGCCUGUG CUGAUGAG X CGAA IGAAGUGA		TCACTTCC C CACAGGCT	
3694	CAGCCUGU CUGAUGAG X CGAA IGGAAGUG		CACTTCCC C ACAGGCTG	
3695	CCAGCCUG CUGAUGAG X CGAA IGGGAAGU		ACTTCCCC A CAGGCTGG	
3697	CGCCAGCC CUGAUGAG X CGAA IUGGGGAA		TTCCCCAC A GGCTGGCG	
3701	CGAGCGCC CUGAUGAG X CGAA ICCUGUGG		CCACAGGC T GGCGCTCG	
3707	UGGAGCCG CUGAUGAG X CGAA ICGCCAGC		GCTGGCGC T CGGCTCCA	
3712	UGGGGUGG CUGAUGAG X CGAA ICCGAGCG		CGCTCGGC T CCACCCCA	
3714	CCUGGGGU CUGAUGAG X CGAA IAGCCGAG		CTCGGCTC C ACCCCAGG	

Table IV

3715	CCCUGGGG CUGAUGAG X CGAA IGAGCCGA		TCGGCTCC A CCCCAGGG	
3717	GGCCCUGG CUGAUGAG X CGAA IUGGAGCC		GGCTCCAC C CCAGGGCC	
3718	UGGCCCUG CUGAUGAG X CGAA IGUGGAGC		GCTCCACC C CAGGGCCA	
3719	CUGGCCCU CUGAUGAG X CGAA IGGUGGAG		CTCCACCC C AGGGCCAG	
3720	GCUGGCCC CUGAUGAG X CGAA IGGGUGGA		TCCACCCC A GGGCCAGC	
3725	GAAAAGCU CUGAUGAG X CGAA ICCCUGGG		CCCAGGGC C AGCTTTTC	
3726	GGAAAAGC CUGAUGAG X CGAA IGCCCUGG		CCAGGGCC A GCTTTTCC	
3729	UGAGGAAA CUGAUGAG X CGAA ICUGGCCC		GGGCCAGC T TTTCCTCA	
3734	CCUGGUGA CUGAUGAG X CGAA IAAAAGCU		AGCTTTTC C TCACCAGG	
3735	UCCUGGUG CUGAUGAG X CGAA IGAAAAGC		GCTTTTCC T CACCAGGA	
3737	GCUCCUGG CUGAUGAG X CGAA IAGGAAAA		TTTTCCTC A CCAGGAGC	
3739	GGGCUCCU CUGAUGAG X CGAA IUGAGGAA		TTCCTCAC C AGGAGCCC	
3740	CGGGCUCC CUGAUGAG X CGAA IGUGAGGA		TCCTCACC A GGAGCCCG	
3746	GGAAGCCG CUGAUGAG X CGAA ICUCCUGG		CCAGGAGC C CGGCTTCC	
3747	UGGAAGCC CUGAUGAG X CGAA IGCUCCUG		CAGGAGCC C GGCTTCCA	
3751	GGAGUGGA CUGAUGAG X CGAA ICCGGGCU		AGCCCGGC T TCCACTCC	
3754	UGGGGAGU CUGAUGAG X CGAA IAAGCCGG		CCGGCTTC C ACTCCCCA	
3755	GUGGGGAG CUGAUGAG X CGAA IGAAGCCG		CGGCTTCC A CTCCCCAC	
3757	AUGUGGGG CUGAUGAG X CGAA IUGGAAGC		GCTTCCAC T CCCCACAT	
3759	CUAUGUGG CUGAUGAG X CGAA IAGUGGAA		TTCCACTC C CCACATAG	
3760	CCUAUGUG CUGAUGAG X CGAA IGAGUGGA		TCCACTCC C CACATAGG	
3761	UCCUAUGU CUGAUGAG X CGAA IGGAGUGG		CCACTCCC C ACATAGGA	
3762	UUCCUAUG CUGAUGAG X CGAA IGGGAGUG		CACTCCCC A CATAGGAA	
3764	UAUUCCUA CUGAUGAG X CGAA IUGGGGAG		CTCCCCAC A TAGGAATA	
3776	CUGGGGAU CUGAUGAG X CGAA IACUAUUC		GAATAGTC C ATCCCCAG	
3777	UCUGGGGA CUGAUGAG X CGAA IGACUAUU		AATAGTCC A TCCCCAGA	
3780	GAAUCUGG CUGAUGAG X CGAA IAUGGACU		AGTCCATC C CCAGATTC	
3781	CGAAUCUG CUGAUGAG X CGAA IGAUGGAC		GTCCATCC C CAGATTCG	
3782	GCGAAUCU CUGAUGAG X CGAA IGGAUGGA		TCCATCCC C AGATTCGC	
3783	GGCGAAUC CUGAUGAG X CGAA IGGGAUGG		CCATCCCC A GATTCGCC	
3791	UGAACAAU CUGAUGAG X CGAA ICGAAUCU		AGATTCGC C ATTGTTCA	
3792	GUGAACAA CUGAUGAG X CGAA IGCGAAUC		GATTCGCC A TTGTTCAC	
3799	GCGAGGGG CUGAUGAG X CGAA IAACAAUG		CATTGTTC A CCCCTCGC	
3801	GGGCGAGG CUGAUGAG X CGAA IUGAACAA		TTGTTCAC C CCTCGCCC	
3802	AGGGCGAG CUGAUGAG X CGAA IGUGAACA		TGTTCACC C CTCGCCCT	
3803	CAGGGCGA CUGAUGAG X CGAA IGGUGAAC		GTTCACCC C TCGCCCTG	
3804	GCAGGGCG CUGAUGAG X CGAA IGGGUGAA		TTCACCCC T CGCCCTGC	
3808	GAGGGCAG CUGAUGAG X CGAA ICGAGGGG		CCCCTCGC C CTGCCCTC	
3809	GGAGGGCA CUGAUGAG X CGAA IGCGAGGG		CCCTCGCC C TGCCCTCC	
3810	AGGAGGGC CUGAUGAG X CGAA IGGCGAGG		CCTCGCCC T GCCCTCCT	
3813	CAAAGGAG CUGAUGAG X CGAA ICAGGGCG		CGCCCTGC C CTCCTTTG	
3814	GCAAAGGA CUGAUGAG X CGAA IGCAGGGC		GCCCTGCC C TCCTTTGC	
3815	GGCAAAGG CUGAUGAG X CGAA IGGCAGGG		CCCTGCCC T CCTTTGCC	
3817	AAGGCAAA CUGAUGAG X CGAA IAGGGCAG		CTGCCCTC C TTTGCCTT	
3818	GAAGGCAA CUGAUGAG X CGAA IGAGGGCA		TGCCCTCC T TTGCCTTC	
3823	GGGUGGAA CUGAUGAG X CGAA ICAAAGGA		TCCTTTGC C TTCCACCC	
3824	GGGGUGGA CUGAUGAG X CGAA IGCAAAGG		CCTTTGCC T TCCACCCC	

Table IV

3827	GUGGGGGU CUGAUGAG X CGAA IAAGGCAA		TTGCCTTC C ACCCCCAC	
3828	GGUGGGGG CUGAUGAG X CGAA IGAAGGCA		TGCCTTCC A CCCCCACC	
3830	AUGGUGGG CUGAUGAG X CGAA IUGGAAGG		CCTTCCAC C CCCACCAT	
3831	GAUGGUGG CUGAUGAG X CGAA IGUGGAAG		CTTCCACC C CCACCATC	
3832	GGAUGGUG CUGAUGAG X CGAA IGGUGGAA		TTCCACCC C CACCATCC	
3833	UGGAUGGU CUGAUGAG X CGAA IGGGUGGA		TCCACCCC C ACCATCCA	
3834	CUGGAUGG CUGAUGAG X CGAA IGGGGUGG		CCACCCCC A CCATCCAG	
3836	ACCUGGAU CUGAUGAG X CGAA IUGGGGGU		ACCCCCAC C ATCCAGGT	
3837	CACCUGGA CUGAUGAG X CGAA IGUGGGGG		CCCCCACC A TCCAGGTG	
3840	CUCCACCU CUGAUGAG X CGAA IAUGGUGG		CCACCATC C AGGTGGAG	
3841	UCUCCACC CUGAUGAG X CGAA IGAUGGUG		CACCATCC A GGTGGAGA	
3851	CUUCUCAG CUGAUGAG X CGAA IUCUCCAC		GTGGAGAC C CTGAGAAG	
3852	CCUUCUCA CUGAUGAG X CGAA IGUCUCCA		TGGAGACC C TGAGAAGG	
3853	UCCUUCUC CUGAUGAG X CGAA IGGUCUCC		GGAGACCC T GAGAAGGA	
3863	GCUCCCAG CUGAUGAG X CGAA IUCCUUCU		AGAAGGAC C CTGGGAGC	
3864	AGCUCCCA CUGAUGAG X CGAA IGUCCUUC		GAAGGACC C TGGGAGCT	
3865	GAGCUCCC CUGAUGAG X CGAA IGGUCCUU		AAGGACCC T GGGAGCTC	
3872	AUUCCCAG CUGAUGAG X CGAA ICUCCCAG		CTGGGAGC T CTGGGAAT	
3874	AAAUUCCC CUGAUGAG X CGAA IAGCUCCC		GGGAGCTC T GGGAATTT	
3891	ACACCUUU CUGAUGAG X CGAA IUCACUCC		GGAGTGAC C AAAGGTGT	
3892	CACACCUU CUGAUGAG X CGAA IGUCACUC		GAGTGACC A AAGGTGTG	
3902	GUGUACAG CUGAUGAG X CGAA ICACACCU		AGGTGTGC C CTGTACAC	
3903	UGUGUACA CUGAUGAG X CGAA IGCACACC		GGTGTGCC C TGTACACA	
3904	CUGUGUAC CUGAUGAG X CGAA IGGCACAC		GTGTGCCC T GTACACAG	
3909	CUCGCCUG CUGAUGAG X CGAA IUACAGGG		CCCTGTAC A CAGGCGAG	
3911	UCCUCGCC CUGAUGAG X CGAA IUGUACAG		CTGTACAC A GGCGAGGA	
3921	AGGUGCAG CUGAUGAG X CGAA IUCCUCGC		GCGAGGAC C CTGCACCT	
3922	CAGGUGCA CUGAUGAG X CGAA IGUCCUCG		CGAGGACC C TGCACCTG	
3923	CCAGGUGC CUGAUGAG X CGAA IGGUCCUC		GAGGACCC T GCACCTGG	
3926	CAUCCAGG CUGAUGAG X CGAA ICAGGGUC		GACCCTGC A CCTGGATG	
3928	CCCAUCCA CUGAUGAG X CGAA IUGCAGGG		CCCTGCAC C TGGATGGG	
3929	CCCCAUCC CUGAUGAG X CGAA IGUGCAGG		CCTGCACC T GGATGGGG	
3941	ACCCACAG CUGAUGAG X CGAA IACCCCCA		TGGGGGTC C CTGTGGGT	
3942	GACCCACA CUGAUGAG X CGAA IGACCCCC		GGGGGTCC C TGTGGGTC	
3943	UGACCCAC CUGAUGAG X CGAA IGGACCCC		GGGGTCCC T GTGGGTCA	
3951	CCCCAAUU CUGAUGAG X CGAA IACCCACA		TGTGGGTC A AATTGGGG	
3968	ACUCCCAC CUGAUGAG X CGAA ICACCUCC		GGAGGTGC T GTGGGAGT	
3984	AUAUAUUC CUGAUGAG X CGAA IUAUUUUA		TAAAATAC T GAATATAT	
4002	UUCAAAAC CUGAUGAG X CGAA IAAAAACU		AGTTTTTC A GTTTTGAA	

Stem Length = 8 . Core Sequence = CUGAUGAG X CGAA (X = GCCGUUAGGC or other stem II sequence and length (greater than or equal to 2 base-pairs)). I = Inosine nucleotide

Seq1 = TERT (Homo sapiens telomerase reverse transcriptase (TERT) mRNA, 4015 bp); Nakamura *et al* , Science 277 (5328), 955-959 (1997)

Table V: Human telomerase reverse transcriptase (TERT) G-Cleaver Ribozyme and Target Sequence

nt. Position	Substrate Sequence	Seq ID Nos	Ribozyme Sequence	Seq ID Nos
16	GCUGCGUCCU G CUGCG		CGCAG UGAUGGCAUGCACUAUGCGCG AGGACGCAGC	
19	GCGUCCUGCU G CGCAC		GUGCG UGAUGGCAUGCACUAUGCGCG AGCAGGACGC	
21	GUCCUGCUGC G CACGU		ACGUG UGAUGGCAUGCACUAUGCGCG GCAGCAGGAC	
53	GGCCACCCCC G CGAUG		CAUCG UGAUGGCAUGCACUAUGCGCG GGGGGUGGCC	
55	CCACCCCCGC G AUGCC		GGCAU UGAUGGCAUGCACUAUGCGCG GCGGGGGUGG	
58	CCCCCGCGAU G CCGCG		CGCGG UGAUGGCAUGCACUAUGCGCG AUCGCGGGGG	
61	CCGCGAUGCC G CGCGC		GCGCG UGAUGGCAUGCACUAUGCGCG GGCAUCGCGG	
63	GCGAUGCCGC G CGCUC		GAGCG UGAUGGCAUGCACUAUGCGCG GCGGCAUCGC	
65	GAUGCCGCGC G CUCCC		GGGAG UGAUGGCAUGCACUAUGCGCG GCGCGGCAUC	
72	CGCGCUCCCC G CUGCC		GGCAG UGAUGGCAUGCACUAUGCGCG GGGGAGCGCG	
75	GCUCCCCGCU G CCGAG		CUCGG UGAUGGCAUGCACUAUGCGCG AGCGGGGAGC	
78	CCCCGCUGCC G AGCCG		CGGCU UGAUGGCAUGCACUAUGCGCG GGCAGCGGGG	
85	GCCGAGCCGU G CGCUC		GAGCG UGAUGGCAUGCACUAUGCGCG ACGGCUCGGC	
87	CGAGCCGUGC G CUCCC		GGGAG UGAUGGCAUGCACUAUGCGCG GCACGGCUCG	
94	UGCGCUCCCU G CUGCG		CGCAG UGAUGGCAUGCACUAUGCGCG AGGGAGCGCA	
97	GCUCCCUGCU G CGCAG		CUGCG UGAUGGCAUGCACUAUGCGCG AGCAGGGAGC	
99	UCCCUGCUGC G CAGCC		GGCUG UGAUGGCAUGCACUAUGCGCG GCAGCAGGGA	
111	AGCCACUACC G CGAGG		CCUCG UGAUGGCAUGCACUAUGCGCG GGUAGUGGCU	
113	CCACUACCGC G AGGUG		CACCU UGAUGGCAUGCACUAUGCGCG GCGGUAGUGG	
118	ACCGCGAGGU G CUGCC		GGCAG UGAUGGCAUGCACUAUGCGCG ACCUCGCGGU	
121	GCGAGGUGCU G CCGCU		AGCGG UGAUGGCAUGCACUAUGCGCG AGCACCUCGC	
124	AGGUGCUGCC G CUGGC		GCCAG UGAUGGCAUGCACUAUGCGCG GGCAGCACCU	
139	CCACGUUCGU G CGGCG		CGCCG UGAUGGCAUGCACUAUGCGCG ACGAACGUGG	
144	UUCGUGCGGC G CCUGG		CCAGG UGAUGGCAUGCACUAUGCGCG GCCGCACGAA	
172	GGCGGCUGGU G CAGCG		CGCUG UGAUGGCAUGCACUAUGCGCG ACCAGCCGCC	
177	CUGGUGCAGC G CGGGG		CCCCG UGAUGGCAUGCACUAUGCGCG GCUGCACCAG	
198	GCGGCUUUCC G CGCGC		GCGCG UGAUGGCAUGCACUAUGCGCG GGAAAGCCGC	
200	GGCUUUCCGC G CGCUG		CAGCG UGAUGGCAUGCACUAUGCGCG GCGGAAAGCC	

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202	CUUUCCGCGC G CUGGU		ACCAG UGAUGGCAUGCACUAUGCGCG GCGCGGAAAG	
216	GUGGCCCAGU G CCUGG		CCAGG UGAUGGCAUGCACUAUGCGCG ACUGGGCCAC	
223	AGUGCCUGGU G UGCGU		ACGCA UGAUGGCAUGCACUAUGCGCG ACCAGGCACU	
225	UGCCUGGUGU G CGUGC		GCACG UGAUGGCAUGCACUAUGCGCG ACACCAGGCA	
229	UGGUGUGCGU G CCCUG		CAGGG UGAUGGCAUGCACUAUGCGCG ACGCACACCA	
239	GCCCUGGGAC G CACGG		CCGUG UGAUGGCAUGCACUAUGCGCG GUCCCAGGGC	
247	ACGCACGGCC G CCCCC		GGGGG UGAUGGCAUGCACUAUGCGCG GGCCGUGCGU	
254	GCCGCCCCCC G CCGCC		GGCGG UGAUGGCAUGCACUAUGCGCG GGGGGGCGGC	
257	GCCCCCCGCC G CCCCC		GGGGG UGAUGGCAUGCACUAUGCGCG GGCGGGGGGC	
270	CCCUCCUUCC G CCAGG		CCUGG UGAUGGCAUGCACUAUGCGCG GGAAGGAGGG	
277	UCCGCCAGGU G UCCUG		CAGGA UGAUGGCAUGCACUAUGCGCG ACCUGGCGGA	
282	CAGGUGUCCU G CCUGA		UCAGG UGAUGGCAUGCACUAUGCGCG AGGACACCUG	
286	UGUCCUGCCU G AAGGA		UCCUU UGAUGGCAUGCACUAUGCGCG AGGCAGGACA	
303	CUGGUGGCCC G AGUGC		GCACU UGAUGGCAUGCACUAUGCGCG GGGCCACCAG	
307	UGGCCCGAGU G CUGCA		UGCAG UGAUGGCAUGCACUAUGCGCG ACUCGGGCCA	
310	CCCGAGUGCU G CAGAG		CUCUG UGAUGGCAUGCACUAUGCGCG AGCACUCGGG	
319	UGCAGAGGCU G UGCGA		UCGCA UGAUGGCAUGCACUAUGCGCG AGCCUCUGCA	
321	CAGAGGCUGU G CGAGC		GCUCG UGAUGGCAUGCACUAUGCGCG ACAGCCUCUG	
323	GAGGCUGUGC G AGCGC		GCGCU UGAUGGCAUGCACUAUGCGCG GCACAGCCUC	
327	CUGUGCGAGC G CGGCG		CGCCG UGAUGGCAUGCACUAUGCGCG GCUCGCACAG	
332	CGAGCGCGGC G CGAAG		CUUCG UGAUGGCAUGCACUAUGCGCG GCCGCGCUCG	
334	AGCGCGGCGC G AAGAA		UUCUU UGAUGGCAUGCACUAUGCGCG GCGCCGCGCU	
343	CGAAGAACGU G CUGGC		GCCAG UGAUGGCAUGCACUAUGCGCG ACGUUCUUCG	
359	CUUCGGCUUC G CGCUG		CAGCG UGAUGGCAUGCACUAUGCGCG GAAGCCGAAG	
361	UCGGCUUCGC G CUGCU		AGCAG UGAUGGCAUGCACUAUGCGCG GCGAAGCCGA	
364	GCUUCGCGCU G CUGGA		UCCAG UGAUGGCAUGCACUAUGCGCG AGCGCGAAGC	
378	GACGGGGCCC G CGGGG		CCCCG UGAUGGCAUGCACUAUGCGCG GGGCCCCGUC	
392	GGGCCCCCCC G AGGCC		GGCCU UGAUGGCAUGCACUAUGCGCG GGGGGGGCCC	
412	CCACCAGCGU G CGCAG		CUGCG UGAUGGCAUGCACUAUGCGCG ACGCUGGUGG	
414	ACCAGCGUGC G CAGCU		AGCUG UGAUGGCAUGCACUAUGCGCG GCACGCUGGU	
424	GCAGCUACCU G CCCAA		UUGGG UGAUGGCAUGCACUAUGCGCG AGGUAGCUGC	

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436	CCAACACGGU G ACCGA		UCGGU UGAUGGCAUGCACUAUGCGCG ACCGUGUUGG	
440	CACGGUGACC G ACGCA		UGCGU UGAUGGCAUGCACUAUGCGCG GGUCACCGUG	
443	GGUGACCGAC G CACUG		CAGUG UGAUGGCAUGCACUAUGCGCG GUCGGUCACC	
448	CCGACGCACU G CGGGG		CCCCG UGAUGGCAUGCACUAUGCGCG AGUGCGUCGG	
472	CGUGGGGGCU G CUGCU		AGCAG UGAUGGCAUGCACUAUGCGCG AGCCCCCACG	
475	GGGGGCUGCU G CUGCG		CGCAG UGAUGGCAUGCACUAUGCGCG AGCAGCCCCC	
478	GGCUGCUGCU G CGCCG		CGGCG UGAUGGCAUGCACUAUGCGCG AGCAGCAGCC	
480	CUGCUGCUGC G CCGCG		CGCGG UGAUGGCAUGCACUAUGCGCG GCAGCAGCAG	
483	CUGCUGCGCC G CGUGG		CCACG UGAUGGCAUGCACUAUGCGCG GGCGCAGCAG	
491	CCGCGUGGGC G ACGAC		GUCGU UGAUGGCAUGCACUAUGCGCG GCCCACGCGG	
494	CGUGGGCGAC G ACGUG		CACGU UGAUGGCAUGCACUAUGCGCG GUCGCCCACG	
499	GCGACGACGU G CUGGU		ACCAG UGAUGGCAUGCACUAUGCGCG ACGUCGUCGC	
511	UGGUUCACCU G CUGGC		GCCAG UGAUGGCAUGCACUAUGCGCG AGGUGAACCA	
519	CUGCUGGCAC G CUGCG		CGCAG UGAUGGCAUGCACUAUGCGCG GUGCCAGCAG	
522	CUGGCACGCU G CGCGC		GCGCG UGAUGGCAUGCACUAUGCGCG AGCGUGCCAG	
524	GGCACGCUGC G CGCUC		GAGCG UGAUGGCAUGCACUAUGCGCG GCAGCGUGCC	
526	CACGCUGCGC G CUCUU		AAGAG UGAUGGCAUGCACUAUGCGCG GCGCAGCGUG	
533	CGCGCUCUUU G UGCUG		CAGCA UGAUGGCAUGCACUAUGCGCG AAAGAGCGCG	
535	CGCUCUUUGU G CUGGU		ACCAG UGAUGGCAUGCACUAUGCGCG ACAAAGAGCG	
552	GCUCCCAGCU G CGCCU		AGGCG UGAUGGCAUGCACUAUGCGCG AGCUGGGAGC	
554	UCCCAGCUGC G CCUAC		GUAGG UGAUGGCAUGCACUAUGCGCG GCAGCUGGGA	
565	CCUACCAGGU G UGCGG		CCGCA UGAUGGCAUGCACUAUGCGCG ACCUGGUAGG	
567	UACCAGGUGU G CGGGC		GCCCG UGAUGGCAUGCACUAUGCGCG ACACCUGGUA	
574	UGUGCGGGCC G CCGCU		AGCGG UGAUGGCAUGCACUAUGCGCG GGCCCGCACA	
577	GCGGGCCGCC G CUGUA		UACAG UGAUGGCAUGCACUAUGCGCG GGCGGCCCGC	
580	GGCCGCCGCU G UACCA		UGGUA UGAUGGCAUGCACUAUGCGCG AGCGGCGGCC	
593	CCAGCUCGGC G CUGCC		GGCAG UGAUGGCAUGCACUAUGCGCG GCCGAGCUGG	
596	GCUCGGCGCU G CCACU		AGUGG UGAUGGCAUGCACUAUGCGCG AGCGCCGAGC	
616	CCCGGCCCCC G CCACA		UGUGG UGAUGGCAUGCACUAUGCGCG GGGGGCCGGG	
623	CCCGCCACAC G CUAGU		ACUAG UGAUGGCAUGCACUAUGCGCG GUGUGGCGGG	
636	AGUGGACCCC G AAGGC		GCCUU UGAUGGCAUGCACUAUGCGCG GGGGUCCACU	

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651	CGUCUGGGAU G CGAAC		GUUCG UGAUGGCAUGCACUAUGCGCG AUCCCAGACG	
653	UCUGGGAUGC G AACGG		CCGUU UGAUGGCAUGCACUAUGCGCG GCAUCCCAGA	
703	CCCUGGGCCU G CCAGC		GCUGG UGAUGGCAUGCACUAUGCGCG AGGCCCAGGG	
716	AGCCCCGGGU G CGAGG		CCUCG UGAUGGCAUGCACUAUGCGCG ACCCGGGGCU	
718	CCCCGGGUGC G AGGAG		CUCCU UGAUGGCAUGCACUAUGCGCG GCACCCGGGG	
726	GCGAGGAGGC G CGGGG		CCCCG UGAUGGCAUGCACUAUGCGCG GCCUCCUCGC	
737	CGGGGGCAGU G CCAGC		GCUGG UGAUGGCAUGCACUAUGCGCG ACUGCCCCCG	
744	AGUGCCAGCC G AAGUC		GACUU UGAUGGCAUGCACUAUGCGCG GGCUGGCACU	
751	GCCGAAGUCU G CCGUU		AACGG UGAUGGCAUGCACUAUGCGCG AGACUUCGGC	
757	GUCUGCCGUU G CCCAA		UUGGG UGAUGGCAUGCACUAUGCGCG AACGGCAGAC	
779	CAGGCGUGGC G CUGCC		GGCAG UGAUGGCAUGCACUAUGCGCG GCCACGCCUG	
782	GCGUGGCGCU G CCCCU		AGGGG UGAUGGCAUGCACUAUGCGCG AGCGCCACGC	
788	CGCUGCCCCU G AGCCG		CGGCU UGAUGGCAUGCACUAUGCGCG AGGGGCAGCG	
802	CGGAGCGGAC G CCCGU		ACGGG UGAUGGCAUGCACUAUGCGCG GUCCGCUCCG	
841	CGGGCAGGAC G CGUGG		CCACG UGAUGGCAUGCACUAUGCGCG GUCCUGCCCG	
850	CGCGUGGACC G AGUGA		UCACU UGAUGGCAUGCACUAUGCGCG GGUCCACGCG	
854	UGGACCGAGU G ACCGU		ACGGU UGAUGGCAUGCACUAUGCGCG ACUCGGUCCA	
867	CGUGGUUUCU G UGUGG		CCACA UGAUGGCAUGCACUAUGCGCG AGAAACCACG	
869	UGGUUUCUGU G UGGUG		CACCA UGAUGGCAUGCACUAUGCGCG ACAGAAACCA	
874	UCUGUGUGGU G UCACC		GGUGA UGAUGGCAUGCACUAUGCGCG ACCACACAGA	
881	GGUGUCACCU G CCAGA		UCUGG UGAUGGCAUGCACUAUGCGCG AGGUGACACC	
890	UGCCAGACCC G CCGAA		UUCGG UGAUGGCAUGCACUAUGCGCG GGGUCUGGCA	
893	CAGACCCGCC G AAGAA		UUCUU UGAUGGCAUGCACUAUGCGCG GGCGGGUCUG	
917	UUUGGAGGGU G CGCUC		GAGCG UGAUGGCAUGCACUAUGCGCG ACCCUCCAAA	
919	UGGAGGGUGC G CUCUC		GAGAG UGAUGGCAUGCACUAUGCGCG GCACCCUCCA	
931	UCUCUGGCAC G CGCCA		UGGCG UGAUGGCAUGCACUAUGCGCG GUGCCAGAGA	
933	UCUGGCACGC G CCACU		AGUGG UGAUGGCAUGCACUAUGCGCG GCGUGCCAGA	
957	UCCGUGGGCC G CCAGC		GCUGG UGAUGGCAUGCACUAUGCGCG GGCCCACGGA	
968	CCAGCACCAC G CGGGC		GCCCG UGAUGGCAUGCACUAUGCGCG GUGGUGCUGG	
988	CAUCCACAUC G CGGCC		GGCCG UGAUGGCAUGCACUAUGCGCG GAUGUGGAUG	
1012	CCUGGGACAC G CCUUG		CAAGG UGAUGGCAUGCACUAUGCGCG GUGUCCCAGG	

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1017	GACACGCCUU G UCCCC		GGGGA UGAUGGCAUGCACUAUGCGCG AAGGCGUGUC	
1027	GUCCCCCGGU G UACGC		GCGUA UGAUGGCAUGCACUAUGCGCG ACCGGGGGAC	
1031	CCCGGUGUAC G CCGAG		CUCGG UGAUGGCAUGCACUAUGCGCG GUACACCGGG	
1034	GGUGUACGCC G AGACC		GGUCU UGAUGGCAUGCACUAUGCGCG GGCGUACACC	
1064	CUCCUCAGGC G ACAAG		CUUGU UGAUGGCAUGCACUAUGCGCG GCCUGAGGAG	
1078	AGGAGCAGCU G CGGCC		GGCCG UGAUGGCAUGCACUAUGCGCG AGCUGCUCCU	
1105	UCAGCUCUCU G AGGCC		GGCCU UGAUGGCAUGCACUAUGCGCG AGAGAGCUGA	
1117	GGCCCAGCCU G ACUGG		CCAGU UGAUGGCAUGCACUAUGCGCG AGGCUGGGCC	
1124	CCUGACUGGC G CUCGG		CCGAG UGAUGGCAUGCACUAUGCGCG GCCAGUCAGG	
1171	GGCCCUGGAU G CCAGG		CCUGG UGAUGGCAUGCACUAUGCGCG AUCCAGGGCC	
1185	GGGACUCCCC G CAGGU		ACCUG UGAUGGCAUGCACUAUGCGCG GGGGAGUCCC	
1192	CCCGCAGGUU G CCCCG		CGGGG UGAUGGCAUGCACUAUGCGCG AACCUGCGGG	
1197	AGGUUGCCCC G CCUGC		GCAGG UGAUGGCAUGCACUAUGCGCG GGGGCAACCU	
1201	UGCCCCGCCU G CCCCA		UGGGG UGAUGGCAUGCACUAUGCGCG AGGCGGGGCA	
1209	CUGCCCCAGC G CUACU		AGUAG UGAUGGCAUGCACUAUGCGCG GCUGGGGCAG	
1222	ACUGGCAAAU G CGGCC		GGCCG UGAUGGCAUGCACUAUGCGCG AUUUGCCAGU	
1231	UGCGGCCCCU G UUUCU		AGAAA UGAUGGCAUGCACUAUGCGCG AGGGGCCGCA	
1243	UUCUGGAGCU G CUUGG		CCAAG UGAUGGCAUGCACUAUGCGCG AGCUCCAGAA	
1256	UGGGAACCAC G CGCAG		CUGCG UGAUGGCAUGCACUAUGCGCG GUGGUUCCCA	
1258	GGAACCACGC G CAGUG		CACUG UGAUGGCAUGCACUAUGCGCG GCGUGGUUCC	
1263	CACGCGCAGU G CCCCU		AGGGG UGAUGGCAUGCACUAUGCGCG ACUGCGCGUG	
1276	CCUACGGGGU G CUCCU		AGGAG UGAUGGCAUGCACUAUGCGCG ACCCCGUAGG	
1288	UCCUCAAGAC G CACUG		CAGUG UGAUGGCAUGCACUAUGCGCG GUCUUGAGGA	
1293	AAGACGCACU G CCCGC		GCGGG UGAUGGCAUGCACUAUGCGCG AGUGCGUCUU	
1297	CGCACUGCCC G CUGCG		CGCAG UGAUGGCAUGCACUAUGCGCG GGGCAGUGCG	
1300	ACUGCCCGCU G CGAGC		GCUCG UGAUGGCAUGCACUAUGCGCG AGCGGGCAGU	
1302	UGCCCGCUGC G AGCUG		CAGCU UGAUGGCAUGCACUAUGCGCG GCAGCGGGCA	
1307	GCUGCGAGCU G CGGUC		GACCG UGAUGGCAUGCACUAUGCGCG AGCUCGCAGC	
1328	AGCAGCCGGU G UCUGU		ACAGA UGAUGGCAUGCACUAUGCGCG ACCGGCUGCU	
1332	GCCGGUGUCU G UGCCC		GGGCA UGAUGGCAUGCACUAUGCGCG AGACACCGGC	
1334	CGGUGUCUGU G CCCGG		CCGGG UGAUGGCAUGCACUAUGCGCG ACAGACACCG	

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1358	CCAGGGCUCU G UGGCG		CGCCA UGAUGGCAUGCACUAUGCGCG AGAGCCCUGG	
1370	GGCGGCCCCC G AGGAG		CUCCU UGAUGGCAUGCACUAUGCGCG GGGGGCCGCC	
1395	GACCCCCGUC G CCUGG		CCAGG UGAUGGCAUGCACUAUGCGCG GACGGGGGUC	
1402	GUCGCCUGGU G CAGCU		AGCUG UGAUGGCAUGCACUAUGCGCG ACCAGGCGAC	
1408	UGGUGCAGCU G CUCCG		CGGAG UGAUGGCAUGCACUAUGCGCG AGCUGCACCA	
1413	CAGCUGCUCC G CCAGC		GCUGG UGAUGGCAUGCACUAUGCGCG GGAGCAGCUG	
1438	CCUGGCAGGU G UACGG		CCGUA UGAUGGCAUGCACUAUGCGCG ACCUGCCAGG	
1450	ACGGCUUCGU G CGGGC		GCCCG UGAUGGCAUGCACUAUGCGCG ACGAAGCCGU	
1458	GUGCGGGCCU G CCUGC		GCAGG UGAUGGCAUGCACUAUGCGCG AGGCCCGCAC	
1462	GGGCCUGCCU G CGCCG		CGGCG UGAUGGCAUGCACUAUGCGCG AGGCAGGCCC	
1464	GCCUGCCUGC G CCGGC		GCCGG UGAUGGCAUGCACUAUGCGCG GCAGGCAGGC	
1474	GCCGGCUGGU G CCCCC		GGGGG UGAUGGCAUGCACUAUGCGCG ACCAGCCGGC	
1505	CAGGCACAAC G AACGC		GCGUU UGAUGGCAUGCACUAUGCGCG GUUGUGCCUG	
1509	CACAACGAAC G CCGCU		AGCGG UGAUGGCAUGCACUAUGCGCG GUUCGUUGUG	
1512	AACGAACGCC G CUUCC		GGAAG UGAUGGCAUGCACUAUGCGCG GGCGUUCGUU	
1556	GGGGAAGCAU G CCAAG		CUUGG UGAUGGCAUGCACUAUGCGCG AUGCUUCCCC	
1567	CCAAGCUCUC G CUGCA		UGCAG UGAUGGCAUGCACUAUGCGCG GAGAGCUUGG	
1570	AGCUCUCGCU G CAGGA		UCCUG UGAUGGCAUGCACUAUGCGCG AGCGAGAGCU	
1579	UGCAGGAGCU G ACGUG		CACGU UGAUGGCAUGCACUAUGCGCG AGCUCCUGCA	
1591	CGUGGAAGAU G AGCGU		ACGCU UGAUGGCAUGCACUAUGCGCG AUCUUCCACG	
1597	AGAUGAGCGU G CGGGA		UCCCG UGAUGGCAUGCACUAUGCGCG ACGCUCAUCU	
1605	GUGCGGGACU G CGCUU		AAGCG UGAUGGCAUGCACUAUGCGCG AGUCCCGCAC	
1607	GCGGGACUGC G CUUGG		CCAAG UGAUGGCAUGCACUAUGCGCG GCAGUCCCGC	
1615	GCGCUUGGCU G CGCAG		CUGCG UGAUGGCAUGCACUAUGCGCG AGCCAAGCGC	
1617	GCUUGGCUGC G CAGGA		UCCUG UGAUGGCAUGCACUAUGCGCG GCAGCCAAGC	
1638	GGGGUUGGCU G UGUUC		GAACA UGAUGGCAUGCACUAUGCGCG AGCCAACCCC	
1640	GGUUGGCUGU G UUCCG		CGGAA UGAUGGCAUGCACUAUGCGCG ACAGCCAACC	
1649	UGUUCCGGCC G CAGAG		CUCUG UGAUGGCAUGCACUAUGCGCG GGCCGGAACA	
1663	AGCACCGUCU G CGUGA		UCACG UGAUGGCAUGCACUAUGCGCG AGACGGUGCU	
1667	CCGUCUGCGU G AGGAG		CUCCU UGAUGGCAUGCACUAUGCGCG ACGCAGACGG	
1690	CCAAGUUCCU G CACUG		CAGUG UGAUGGCAUGCACUAUGCGCG AGGAACUUGG	

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1699	UGCACUGGCU G AUGAG		CUCAU UGAUGGCAUGCACUAUGCGCG AGCCAGUGCA	
1702	ACUGGCUGAU G AGUGU		ACACU UGAUGGCAUGCACUAUGCGCG AUCAGCCAGU	
1706	GCUGAUGAGU G UGUAC		GUACA UGAUGGCAUGCACUAUGCGCG ACUCAUCAGC	
1708	UGAUGAGUGU G UACGU		ACGUA UGAUGGCAUGCACUAUGCGCG ACACUCAUCA	
1718	GUACGUCGUC G AGCUG		CAGCU UGAUGGCAUGCACUAUGCGCG GACGACGUAC	
1723	UCGUCGAGCU G CUCAG		CUGAG UGAUGGCAUGCACUAUGCGCG AGCUCGACGA	
1742	UUUCUUUUAU G UCACG		CGUGA UGAUGGCAUGCACUAUGCGCG AUAAAAGAAA	
1793	CCGGAAGAGU G UCUGG		CCAGA UGAUGGCAUGCACUAUGCGCG ACUCUUCCGG	
1807	GGAGCAAGUU G CAAAG		CUUUG UGAUGGCAUGCACUAUGCGCG AACUUGCUCC	
1834	GACAGCACUU G AAGAG		CUCUU UGAUGGCAUGCACUAUGCGCG AAGUGCUGUC	
1843	UGAAGAGGGU G CAGCU		AGCUG UGAUGGCAUGCACUAUGCGCG ACCCUCUUCA	
1849	GGGUGCAGCU G CGGGA		UCCCG UGAUGGCAUGCACUAUGCGCG AGCUGCACCC	
1858	UGCGGGAGCU G UCGGA		UCCGA UGAUGGCAUGCACUAUGCGCG AGCUCCCGCA	
1898	AGCCAGGCCC G CCCUG		CAGGG UGAUGGCAUGCACUAUGCGCG GGGCCUGGCU	
1903	GGCCCGCCCU G CUGAC		GUCAG UGAUGGCAUGCACUAUGCGCG AGGGCGGGCC	
1906	CCGCCCUGCU G ACGUC		GACGU UGAUGGCAUGCACUAUGCGCG AGCAGGGCGG	
1920	UCCAGACUCC G CUUCA		UGAAG UGAUGGCAUGCACUAUGCGCG GGAGUCUGGA	
1937	CCCCAAGCCU G ACGGG		CCCGU UGAUGGCAUGCACUAUGCGCG AGGCUUGGGG	
1945	CUGACGGGCU G CGGCC		GGCCG UGAUGGCAUGCACUAUGCGCG AGCCCGUCAG	
1951	GGCUGCGGCC G AUUGU		ACAAU UGAUGGCAUGCACUAUGCGCG GGCCGCAGCC	
1955	GCGGCCGAUU G UGAAC		GUUCA UGAUGGCAUGCACUAUGCGCG AAUCGGCCGC	
1957	GGCCGAUUGU G AACAU		AUGUU UGAUGGCAUGCACUAUGCGCG ACAAUCGGCC	
1992	AGAACGUUCC G CAGAG		CUCUG UGAUGGCAUGCACUAUGCGCG GGAACGUUCU	
2009	AAAGAGGGCC G AGCGU		ACGCU UGAUGGCAUGCACUAUGCGCG GGCCCUCUUU	
2023	GUCUCACCUC G AGGGU		ACCCU UGAUGGCAUGCACUAUGCGCG GAGGUGAGAC	
2029	CCUCGAGGGU G AAGGC		GCCUU UGAUGGCAUGCACUAUGCGCG ACCCUCGAGG	
2038	UGAAGGCACU G UUCAG		CUGAA UGAUGGCAUGCACUAUGCGCG AGUGCCUUCA	
2047	UGUUCAGCGU G CUCAA		UUGAG UGAUGGCAUGCACUAUGCGCG ACGCUGAACA	
2057	GCUCAACUAC G AGCGG		CCGCU UGAUGGCAUGCACUAUGCGCG GUAGUUGAGC	
2065	ACGAGCGGGC G CGGCG		CGCCG UGAUGGCAUGCACUAUGCGCG GCCCGCUCGU	
2070	CGGGCGCGGC G CCCCG		CGGGG UGAUGGCAUGCACUAUGCGCG GCCGCGCCCG	

Table V

2087	CCUCCUGGGC G CCUCU		AGAGG UGAUGGCAUGCACUAUGCGCG GCCCAGGAGG	
2093	GGGCGCCUCU G UGCUG		CAGCA UGAUGGCAUGCACUAUGCGCG AGAGGCGCCC	
2095	GCGCCUCUGU G CUGGG		CCCAG UGAUGGCAUGCACUAUGCGCG ACAGAGGCGC	
2108	GGGCCUGGAC G AUAUC		GAUAU UGAUGGCAUGCACUAUGCGCG GUCCAGGCCC	
2127	AGGGCCUGGC G CACCU		AGGUG UGAUGGCAUGCACUAUGCGCG GCCAGGCCCU	
2137	GCACCUUCGU G CUGCG		CGCAG UGAUGGCAUGCACUAUGCGCG ACGAAGGUGC	
2140	CCUUCGUGCU G CGUGU		ACACG UGAUGGCAUGCACUAUGCGCG AGCACGAAGG	
2144	CGUGCUGCGU G UGCGG		CCGCA UGAUGGCAUGCACUAUGCGCG ACGCAGCACG	
2146	UGCUGCGUGU G CGGGC		GCCCG UGAUGGCAUGCACUAUGCGCG ACACGCAGCA	
2161	CCCAGGACCC G CCGCC		GGCGG UGAUGGCAUGCACUAUGCGCG GGGUCCUGGG	
2164	AGGACCCGCC G CCUGA		UCAGG UGAUGGCAUGCACUAUGCGCG GGCGGGUCCU	
2168	CCCGCCGCCU G AGCUG		CAGCU UGAUGGCAUGCACUAUGCGCG AGGCGGCGGG	
2173	CGCCUGAGCU G UACUU		AAGUA UGAUGGCAUGCACUAUGCGCG AGCUCAGGCG	
2180	GCUGUACUUU G UCAAG		CUUGA UGAUGGCAUGCACUAUGCGCG AAAGUACAGC	
2192	CAAGGUGGAU G UGACG		CGUCA UGAUGGCAUGCACUAUGCGCG AUCCACCUUG	
2194	AGGUGGAUGU G ACGGG		CCCGU UGAUGGCAUGCACUAUGCGCG ACAUCCACCU	
2201	UGUGACGGGC G CGUAC		GUACG UGAUGGCAUGCACUAUGCGCG GCCCGUCACA	
2207	GGGCGCGUAC G ACACC		GGUGU UGAUGGCAUGCACUAUGCGCG GUACGCGCCC	
2243	GGAGGUCAUC G CCAGC		GCUGG UGAUGGCAUGCACUAUGCGCG GAUGACCUCC	
2274	AACACGUACU G CGUGC		GCACG UGAUGGCAUGCACUAUGCGCG AGUACGUGUU	
2278	CGUACUGCGU G CGUCG		CGACG UGAUGGCAUGCACUAUGCGCG ACGCAGUACG	
2288	GCGUCGGUAU G CCGUG		CACGG UGAUGGCAUGCACUAUGCGCG AUACCGACGC	
2306	CCAGAAGGCC G CCCAU		AUGGG UGAUGGCAUGCACUAUGCGCG GGCCUUCUGG	
2322	GGGCACGUCC G CAAGG		CCUUG UGAUGGCAUGCACUAUGCGCG GGACGUGCCC	
2353	UCUCUACCUU G ACAGA		UCUGU UGAUGGCAUGCACUAUGCGCG AAGGUAGAGA	
2374	AGCCGUACAU G CGACA		UGUCG UGAUGGCAUGCACUAUGCGCG AUGUACGGCU	
2376	CCGUACAUGC G ACAGU		ACUGU UGAUGGCAUGCACUAUGCGCG GCAUGUACGG	
2395	UGGCUCACCU G CAGGA		UCCUG UGAUGGCAUGCACUAUGCGCG AGGUGAGCCA	
2410	AGACCAGCCC G CUGAG		CUCAG UGAUGGCAUGCACUAUGCGCG GGGCUGGUCU	
2413	CCAGCCCGCU G AGGGA		UCCCU UGAUGGCAUGCACUAUGCGCG AGCGGGCUGG	
2420	GCUGAGGGAU G CCGUC		GACGG UGAUGGCAUGCACUAUGCGCG AUCCCUCAGC	

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2432	CGUCGUCAUC G AGCAG		CUGCU UGAUGGCAUGCACUAUGCGCG GAUGACGACG	
2449	GCUCCUCCCU G AAUGA		UCAUU UGAUGGCAUGCACUAUGCGCG AGGGAGGAGC	
2453	CUCCCUGAAU G AGGCC		GGCCU UGAUGGCAUGCACUAUGCGCG AUUCAGGGAG	
2474	UGGCCUCUUC G ACGUC		GACGU UGAUGGCAUGCACUAUGCGCG GAAGAGGCCA	
2487	GUCUUCCUAC G CUUCA		UGAAG UGAUGGCAUGCACUAUGCGCG GUAGGAAGAC	
2494	UACGCUUCAU G UGCCA		UGGCA UGAUGGCAUGCACUAUGCGCG AUGAAGCGUA	
2496	CGCUUCAUGU G CCACC		GGUGG UGAUGGCAUGCACUAUGCGCG ACAUGAAGCG	
2504	GUGCCACCAC G CCGUG		CACGG UGAUGGCAUGCACUAUGCGCG GUGGUGGCAC	
2509	ACCACGCCGU G CGCAU		AUGCG UGAUGGCAUGCACUAUGCGCG ACGGCGUGGU	
2511	CACGCCGUGC G CAUCA		UGAUG UGAUGGCAUGCACUAUGCGCG GCACGGCGUG	
2538	UACGUCCAGU G CCAGG		CCUGG UGAUGGCAUGCACUAUGCGCG ACUGGACGUA	
2551	AGGGGAUCCC G CAGGG		CCCUG UGAUGGCAUGCACUAUGCGCG GGGAUCCCCU	
2572	UCCUCUCCAC G CUGCU		AGCAG UGAUGGCAUGCACUAUGCGCG GUGGAGAGGA	
2575	UCUCCACGCU G CUCUG		CAGAG UGAUGGCAUGCACUAUGCGCG AGCGUGGAGA	
2580	ACGCUGCUCU G CAGCC		GGCUG UGAUGGCAUGCACUAUGCGCG AGAGCAGCGU	
2587	UCUGCAGCCU G UGCUA		UAGCA UGAUGGCAUGCACUAUGCGCG AGGCUGCAGA	
2589	UGCAGCCUGU G CUACG		CGUAG UGAUGGCAUGCACUAUGCGCG ACAGGCUGCA	
2597	GUGCUACGGC G ACAUG		CAUGU UGAUGGCAUGCACUAUGCGCG GCCGUAGCAC	
2614	AGAACAAGCU G UUUGC		GCAAA UGAUGGCAUGCACUAUGCGCG AGCUUGUUCU	
2618	CAAGCUGUUU G CGGGG		CCCCG UGAUGGCAUGCACUAUGCGCG AAACAGCUUG	
2641	GGGACGGGCU G CUCCU		AGGAG UGAUGGCAUGCACUAUGCGCG AGCCCGUCCC	
2647	GGCUGCUCCU G CGUUU		AAACG UGAUGGCAUGCACUAUGCGCG AGGAGCAGCC	
2660	UUUGGUGGAU G AUUUC		GAAAU UGAUGGCAUGCACUAUGCGCG AUCCACCAAA	
2668	AUGAUUUCUU G UUGGU		ACCAA UGAUGGCAUGCACUAUGCGCG AAGAAAUCAU	
2674	UCUUGUUGGU G ACACC		GGUGU UGAUGGCAUGCACUAUGCGCG ACCAACAAGA	
2693	CCUCACCCAC G CGAAA		UUUCG UGAUGGCAUGCACUAUGCGCG GUGGGUGAGG	
2695	UCACCCACGC G AAAAC		GUUUU UGAUGGCAUGCACUAUGCGCG GCGUGGGUGA	
2721	ACCCUGGUCC G AGGUG		CACCU UGAUGGCAUGCACUAUGCGCG GGACCAGGGU	
2726	GGUCCGAGGU G UCCCU		AGGGA UGAUGGCAUGCACUAUGCGCG ACCUCGGACC	
2732	AGGUGUCCCU G AGUAU		AUACU UGAUGGCAUGCACUAUGCGCG AGGGACACCU	
2742	GAGUAUGGCU G CGUGG		CCACG UGAUGGCAUGCACUAUGCGCG AGCCAUACUC	

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2749	GCUGCGUGGU G AACUU		AAGUU UGAUGGCAUGCACUAUGCGCG ACCACGCAGC	
2755	UGGUGAACUU G CGGAA		UUCCG UGAUGGCAUGCACUAUGCGCG AAGUUCACCA	
2770	AGACAGUGGU G AACUU		AAGUU UGAUGGCAUGCACUAUGCGCG ACCACUGUCU	
2780	GAACUUCCCU G UAGAA		UUCUA UGAUGGCAUGCACUAUGCGCG AGGGAAGUUC	
2789	UGUAGAAGAC G AGGCC		GGCCU UGAUGGCAUGCACUAUGCGCG GUCUUCUACA	
2813	CACGGCUUUU G UUCAG		CUGAA UGAUGGCAUGCACUAUGCGCG AAAAGCCGUG	
2821	UUGUUCAGAU G CCGGC		GCCGG UGAUGGCAUGCACUAUGCGCG AUCUGAACAA	
2847	UUCCCCUGGU G CGGCC		GGCCG UGAUGGCAUGCACUAUGCGCG ACCAGGGGAA	
2854	GGUGCGGCCU G CUGCU		AGCAG UGAUGGCAUGCACUAUGCGCG AGGCCGCACC	
2857	GCGGCCUGCU G CUGGA		UCCAG UGAUGGCAUGCACUAUGCGCG AGCAGGCCGC	
2881	CCCUGGAGGU G CAGAG		CUCUG UGAUGGCAUGCACUAUGCGCG ACCUCCAGGG	
2888	GGUGCAGAGC G ACUAC		GUAGU UGAUGGCAUGCACUAUGCGCG GCUCUGCACC	
2903	CUCCAGCUAU G CCCGG		CCGGG UGAUGGCAUGCACUAUGCGCG AUAGCUGGAG	
2940	ACCUUCAACC G CGGCU		AGCCG UGAUGGCAUGCACUAUGCGCG GGUUGAAGGU	
2965	GGAGGAACAU G CGUCG		CGACG UGAUGGCAUGCACUAUGCGCG AUGUUCCUCC	
2970	AACAUGCGUC G CAAAC		GUUUG UGAUGGCAUGCACUAUGCGCG GACGCAUGUU	
2989	UUGGGGUCUU G CGGCU		AGCCG UGAUGGCAUGCACUAUGCGCG AAGACCCCAA	
2995	UCUUGCGGCU G AAGUG		CACUU UGAUGGCAUGCACUAUGCGCG AGCCGCAAGA	
3000	CGGCUGAAGU G UCACA		UGUGA UGAUGGCAUGCACUAUGCGCG ACUUCAGCCG	
3010	GUCACAGCCU G UUUCU		AGAAA UGAUGGCAUGCACUAUGCGCG AGGCUGUGAC	
3022	UUCUGGAUUU G CAGGU		ACCUG UGAUGGCAUGCACUAUGCGCG AAAUCCAGAA	
3028	AUUUGCAGGU G AACAG		CUGUU UGAUGGCAUGCACUAUGCGCG ACCUGCAAAU	
3046	UCCAGACGGU G UGCAC		GUGCA UGAUGGCAUGCACUAUGCGCG ACCGUCUGGA	
3048	CAGACGGUGU G CACCA		UGGUG UGAUGGCAUGCACUAUGCGCG ACACCGUCUG	
3073	AGAUCCUCCU G CUGCA		UGCAG UGAUGGCAUGCACUAUGCGCG AGGAGGAUCU	
3076	UCCUCCUGCU G CAGGC		GCCUG UGAUGGCAUGCACUAUGCGCG AGCAGGAGGA	
3095	CAGGUUUCAC G CAUGU		ACAUG UGAUGGCAUGCACUAUGCGCG GUGAAACCUG	
3099	UUUCACGCAU G UGUGC		GCACA UGAUGGCAUGCACUAUGCGCG AUGCGUGAAA	
3101	UCACGCAUGU G UGCUG		CAGCA UGAUGGCAUGCACUAUGCGCG ACAUGCGUGA	
3103	ACGCAUGUGU G CUGCA		UGCAG UGAUGGCAUGCACUAUGCGCG ACACAUGCGU	
3106	CAUGUGUGCU G CAGCU		AGCUG UGAUGGCAUGCACUAUGCGCG AGCACACAUG	

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3154	CAUUUUUCCU G CGCGU		ACGCG UGAUGGCAUGCACUAUGCGCG AGGAAAAAUG	
3156	UUUUUCCUGC G CGUCA		UGACG UGAUGGCAUGCACUAUGCGCG GCAGGAAAAA	
3167	CGUCAUCUCU G ACACG		CGUGU UGAUGGCAUGCACUAUGCGCG AGAGAUGACG	
3183	GCCUCCCUCU G CUACU		AGUAG UGAUGGCAUGCACUAUGCGCG AGAGGGAGGC	
3196	ACUCCAUCCU G AAAGC		GCUUU UGAUGGCAUGCACUAUGCGCG AGGAUGGAGU	
3209	AGCCAAGAAC G CAGGG		CCCUG UGAUGGCAUGCACUAUGCGCG GUUCUUGGCU	
3217	ACGCAGGGAU G UCGCU		AGCGA UGAUGGCAUGCACUAUGCGCG AUCCCUGCGU	
3220	CAGGGAUGUC G CUGGG		CCCAG UGAUGGCAUGCACUAUGCGCG GACAUCCCUG	
3236	GGCCAAGGGC G CCGCC		GGCGG UGAUGGCAUGCACUAUGCGCG GCCCUUGGCC	
3239	CAAGGGCGCC G CCGGC		GCCGG UGAUGGCAUGCACUAUGCGCG GGCGCCCUUG	
3250	CCGGCCCUCU G CCCUC		GAGGG UGAUGGCAUGCACUAUGCGCG AGAGGGCCGG	
3257	UCUGCCCUCC G AGGCC		GGCCU UGAUGGCAUGCACUAUGCGCG GGAGGGCAGA	
3265	CCGAGGCCGU G CAGUG		CACUG UGAUGGCAUGCACUAUGCGCG ACGGCCUCGG	
3274	UGCAGUGGCU G UGCCA		UGGCA UGAUGGCAUGCACUAUGCGCG AGCCACUGCA	
3276	CAGUGGCUGU G CCACC		GGUGG UGAUGGCAUGCACUAUGCGCG ACAGCCACUG	
3292	AAGCAUUCCU G CUCAA		UUGAG UGAUGGCAUGCACUAUGCGCG AGGAAUGCUU	
3301	UGCUCAAGCU G ACUCG		CGAGU UGAUGGCAUGCACUAUGCGCG AGCUUGAGCA	
3306	AAGCUGACUC G ACACC		GGUGU UGAUGGCAUGCACUAUGCGCG GAGUCAGCUU	
3314	UCGACACCGU G UCACC		GGUGA UGAUGGCAUGCACUAUGCGCG ACGGUGUCGA	
3325	UCACCUACGU G CCACU		AGUGG UGAUGGCAUGCACUAUGCGCG ACGUAGGUGA	
3358	CAGCCCAGAC G CAGCU		AGCUG UGAUGGCAUGCACUAUGCGCG GUCUGGGCUG	
3364	AGACGCAGCU G AGUCG		CGACU UGAUGGCAUGCACUAUGCGCG AGCUGCGUCU	
3385	UCCCGGGGAC G ACGCU		AGCGU UGAUGGCAUGCACUAUGCGCG GUCCCCGGGA	
3388	CGGGGACGAC G CUGAC		GUCAG UGAUGGCAUGCACUAUGCGCG GUCGUCCCCG	
3391	GGACGACGCU G ACUGC		GCAGU UGAUGGCAUGCACUAUGCGCG AGCGUCGUCC	
3395	GACGCUGACU G CCCUG		CAGGG UGAUGGCAUGCACUAUGCGCG AGUCAGCGUC	
3407	CCUGGAGGCC G CAGCC		GGCUG UGAUGGCAUGCACUAUGCGCG GGCCUCCAGG	
3424	ACCCGGCACU G CCCUC		GAGGG UGAUGGCAUGCACUAUGCGCG AGUGCCGGGU	
3453	AUCCUGGACU G AUGGC		GCCAU UGAUGGCAUGCACUAUGCGCG AGUCCAGGAU	
3464	AUGGCCACCC G CCCAC		GUGGG UGAUGGCAUGCACUAUGCGCG GGGUGGCCAU	
3479	CAGCCAGGCC G AGAGC		GCUCU UGAUGGCAUGCACUAUGCGCG GGCCUGGCUG	

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3501	CAGCAGCCCU G UCACG		CGUGA UGAUGGCAUGCACUAUGCGCG AGGGCUGCUG	
3506	GCCCUGUCAC G CCGGG		CCCGG UGAUGGCAUGCACUAUGCGCG GUGACAGGGC	
3554	ACCCAGGCCC G CACCG		CGGUG UGAUGGCAUGCACUAUGCGCG GGGCCUGGGU	
3559	GGCCCGCACC G CUGGG		CCCAG UGAUGGCAUGCACUAUGCGCG GGUGCGGGCC	
3570	CUGGGAGUCU G AGGCC		GGCCU UGAUGGCAUGCACUAUGCGCG AGACUCCCAG	
3577	UCUGAGGCCU G AGUGA		UCACU UGAUGGCAUGCACUAUGCGCG AGGCCUCAGA	
3581	AGGCCUGAGU G AGUGU		ACACU UGAUGGCAUGCACUAUGCGCG ACUCAGGCCU	
3585	CUGAGUGAGU G UUUGG		CCAAA UGAUGGCAUGCACUAUGCGCG ACUCACUCAG	
3593	GUGUUUGGCC G AGGCC		GGCCU UGAUGGCAUGCACUAUGCGCG GGCCAAACAC	
3600	GCCGAGGCCU G CAUGU		ACAUG UGAUGGCAUGCACUAUGCGCG AGGCCUCGGC	
3604	AGGCCUGCAU G UCCGG		CCGGA UGAUGGCAUGCACUAUGCGCG AUGCAGGCCU	
3612	AUGUCCGGCU G AAGGC		GCCUU UGAUGGCAUGCACUAUGCGCG AGCCGGACAU	
3619	GCUGAAGGCU G AGUGU		ACACU UGAUGGCAUGCACUAUGCGCG AGCCUUCAGC	
3623	AAGGCUGAGU G UCCGG		CCGGA UGAUGGCAUGCACUAUGCGCG ACUCAGCCUU	
3631	GUGUCCGGCU G AGGCC		GGCCU UGAUGGCAUGCACUAUGCGCG AGCCGGACAC	
3638	GCUGAGGCCU G AGCGA		UCGCU UGAUGGCAUGCACUAUGCGCG AGGCCUCAGC	
3642	AGGCCUGAGC G AGUGU		ACACU UGAUGGCAUGCACUAUGCGCG GCUCAGGCCU	
3646	CUGAGCGAGU G UCCAG		CUGGA UGAUGGCAUGCACUAUGCGCG ACUCGCUCAG	
3661	GCCAAGGGCU G AGUGU		ACACU UGAUGGCAUGCACUAUGCGCG AGCCCUUGGC	
3665	AGGGCUGAGU G UCCAG		CUGGA UGAUGGCAUGCACUAUGCGCG ACUCAGCCCU	
3678	CAGCACACCU G CCGUC		GACGG UGAUGGCAUGCACUAUGCGCG AGGUGUGCUG	
3705	ACAGGCUGGC G CUCGG		CCGAG UGAUGGCAUGCACUAUGCGCG GCCAGCCUGU	
3789	CCCCAGAUUC G CCAUU		AAUGG UGAUGGCAUGCACUAUGCGCG GAAUCUGGGG	
3795	AUUCGCCAUU G UUCAC		GUGAA UGAUGGCAUGCACUAUGCGCG AAUGGCGAAU	
3806	UUCACCCCUC G CCCUG		CAGGG UGAUGGCAUGCACUAUGCGCG GAGGGGUGAA	
3811	CCCUCGCCCU G CCCUC		GAGGG UGAUGGCAUGCACUAUGCGCG AGGGCGAGGG	
3821	GCCCUCCUUU G CCUUC		GAAGG UGAUGGCAUGCACUAUGCGCG AAAGGAGGGC	
3854	UGGAGACCCU G AGAAG		CUUCU UGAUGGCAUGCACUAUGCGCG AGGGUCUCCA	
3888	AAUUUGGAGU G ACCAA		UUGGU UGAUGGCAUGCACUAUGCGCG ACUCCAAAUU	
3898	GACCAAAGGU G UGCCC		GGGCA UGAUGGCAUGCACUAUGCGCG ACCUUUGGUC	
3900	CCAAAGGUGU G CCCUG		CAGGG UGAUGGCAUGCACUAUGCGCG ACACCUUUGG	

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3905	GGUGUGCCCU G UACAC		GUGUA UGAUGGCAUGCACUAUGCGCG AGGGCACACC	
3915	GUACACAGGC G AGGAC		GUCCU UGAUGGCAUGCACUAUGCGCG GCCUGUGUAC	
3924	CGAGGACCCU G CACCU		AGGUG UGAUGGCAUGCACUAUGCGCG AGGGUCCUCG	
3944	GGGGGUCCCU G UGGGU		ACCCA UGAUGGCAUGCACUAUGCGCG AGGGACCCCC	
3966	GGGGGGAGGU G CUGUG		CACAG UGAUGGCAUGCACUAUGCGCG ACCUCCCCCC	
3969	GGGAGGUGCU G UGGGA		UCCCA UGAUGGCAUGCACUAUGCGCG AGCACCUCCC	
3985	GUAAAAUACU G AAUAU		AUAUU UGAUGGCAUGCACUAUGCGCG AGUAUUUUAC	
3993	CUGAAUAUAU G AGUUU		AAACU UGAUGGCAUGCACUAUGCGCG AUAUAUUCAG	
4008	UUUCAGUUUU G AAAAA		UUUUU UGAUGGCAUGCACUAUGCGCG AAAACUGAAA	

Seq1 = TERT (Homo sapiens telomerase reverse transcriptase (TERT) mRNA, 4015 bp); Nakamura *et al.*, Science 277 (5328), 955-959 (1997)
Input Sequence = TERT. Cut Site = YG/M or UG/U.
Stem Length = 5/10. Core Sequence = UGAUG GCAUGCACUAUGC GCG

Table VI: Human telomerase reverse transcriptase (TERT) DNAzyme and Target Sequence

nt. Position	DNAzyme Sequence	Seq. ID Nos	Substrate	Seq. ID Nos
9	CAGGACGC GGCTAGCTACAACGA AGCGCTGC		GCAGCGCT G GCGTCCTG	
11	AGCAGGAC GGCTAGCTACAACGA GCAGCGCT		AGCGCTGC G GTCCTGCT	
16	TGCGCAGC GGCTAGCTACAACGA AGGACGCA		TGCGTCCT G GCTGCGCA	
19	ACGTGCGC GGCTAGCTACAACGA AGCAGGAC		GTCCTGCT G GCGCACGT	
21	CCACGTGC GGCTAGCTACAACGA GCAGCAGG		CCTGCTGC G GCACGTGG	
23	TCCCACGT GGCTAGCTACAACGA GCGCAGCA		TGCTGCGC A ACGTGGGA	
25	CTTCCCAC GGCTAGCTACAACGA GTGCGCAG		CTGCGCAC G GTGGGAAG	
32	GCCAGGGC GGCTAGCTACAACGA TTCCCACG		CGTGGGAA G GCCCTGGC	
38	GCCGGGGC GGCTAGCTACAACGA CAGGGCTT		AAGCCCTG G GCCCCGGC	
44	GGGGTGGC GGCTAGCTACAACGA CGGGGCCA		TGGCCCCG G GCCACCCC	
47	GCGGGGGT GGCTAGCTACAACGA GGCCGGGG		CCCCGGCC A ACCCCCGC	
53	GGCATCGC GGCTAGCTACAACGA GGGGGTGG		CCACCCCC G GCGATGCC	
56	CGCGGCAT GGCTAGCTACAACGA CGCGGGGG		CCCCCGCG A ATGCCGCG	
58	CGCGCGGC GGCTAGCTACAACGA ATCGCGGG		CCCGCGAT G GCCGCGCG	
61	GAGCGCGC GGCTAGCTACAACGA GGCATCGC		GCGATGCC G GCGCGCTC	
63	GGGAGCGC GGCTAGCTACAACGA GCGGCATC		GATGCCGC G GCGCTCCC	
65	CGGGGAGC GGCTAGCTACAACGA GCGCGGCA		TGCCGCGC G GCTCCCCG	
72	TCGGCAGC GGCTAGCTACAACGA GGGGAGCG		CGCTCCCC G GCTGCCGA	
75	GGCTCGGC GGCTAGCTACAACGA AGCGGGGA		TCCCCGCT G GCCGAGCC	
80	CGCACGGC GGCTAGCTACAACGA TCGGCAGC		GCTGCCGA G GCCGTGCG	
83	GAGCGCAC GGCTAGCTACAACGA GGCTCGGC		GCCGAGCC G GTGCGCTC	
85	GGGAGCGC GGCTAGCTACAACGA ACGGCTCG		CGAGCCGT G GCGCTCCC	
87	CAGGGAGC GGCTAGCTACAACGA GCACGGCT		AGCCGTGC G GCTCCCTG	
94	TGCGCAGC GGCTAGCTACAACGA AGGGAGCG		CGCTCCCT G GCTGCGCA	
97	GGCTGCGC GGCTAGCTACAACGA AGCAGGGA		TCCCTGCT G GCGCAGCC	
99	GTGGCTGC GGCTAGCTACAACGA GCAGCAGG		CCTGCTGC G GCAGCCAC	
102	GTAGTGGC GGCTAGCTACAACGA TGCGCAGC		GCTGCGCA G GCCACTAC	

105	GCGGTAGT GGCTAGCTACAACGA GGCTGCGC		GCGCAGCC A ACTACCGC	
108	CTCGCGGT GGCTAGCTACAACGA AGTGGCTG		CAGCCACT A ACCGCGAG	
111	CACCTCGC GGCTAGCTACAACGA GGTAGTGG		CCACTACC G GCGAGGTG	
116	GGCAGCAC GGCTAGCTACAACGA CTCGCGGT		ACCGCGAG G GTGCTGCC	
118	GCGGCAGC GGCTAGCTACAACGA ACCTCGCG		CGCGAGGT G GCTGCCGC	
121	CCAGCGGC GGCTAGCTACAACGA AGCACCTC		GAGGTGCT G GCCGCTGG	
124	TGGCCAGC GGCTAGCTACAACGA GGCAGCAC		GTGCTGCC G GCTGGCCA	
128	AACGTGGC GGCTAGCTACAACGA CAGCGGCA		TGCCGCTG G GCCACGTT	
131	ACGAACGT GGCTAGCTACAACGA GGCCAGCG		CGCTGGCC A ACGTTCGT	
133	GCACGAAC GGCTAGCTACAACGA GTGGCCAG		CTGGCCAC G GTTCGTGC	
137	CGCCGCAC GGCTAGCTACAACGA GAACGTGG		CCACGTTC G GTGCGGCG	
139	GGCGCCGC GGCTAGCTACAACGA ACGAACGT		ACGTTCGT G GCGGCGCC	
142	CCAGGCGC GGCTAGCTACAACGA CGCACGAA		TTCGTGCG G GCGCCTGG	
144	CCCCAGGC GGCTAGCTACAACGA GCCGCACG		CGTGCGGC G GCCTGGGG	
151	CCTGGGGC GGCTAGCTACAACGA CCCAGGCG		CGCCTGGG G GCCCCAGG	
159	CCGCCAGC GGCTAGCTACAACGA CCTGGGGC		GCCCCAGG G GCTGGCGG	
163	CCAGCCGC GGCTAGCTACAACGA CAGCCCTG		CAGGGCTG G GCGGCTGG	
166	GCACCAGC GGCTAGCTACAACGA CGCCAGCC		GGCTGGCG G GCTGGTGC	
170	CGCTGCAC GGCTAGCTACAACGA CAGCCGCC		GGCGGCTG G GTGCAGCG	
172	CGCGCTGC GGCTAGCTACAACGA ACCAGCCG		CGGCTGGT G GCAGCGCG	
175	CCCCGCGC GGCTAGCTACAACGA TGCACCAG		CTGGTGCA G GCGCGGGG	
177	GTCCCCGC GGCTAGCTACAACGA GCTGCACC		GGTGCAGC G GCGGGGAC	
183	CGCCGGGT GGCTAGCTACAACGA CCCCGCGC		GCGCGGGG A ACCCGGCG	
188	AAAGCCGC GGCTAGCTACAACGA CGGGTCCC		GGGACCCG G GCGGCTTT	
191	CGGAAAGC GGCTAGCTACAACGA CGCCGGGT		ACCCGGCG G GCTTTCCG	
198	CAGCGCGC GGCTAGCTACAACGA GGAAAGCC		GGCTTTCC G GCGCGCTG	
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1276	TGAGGAGC GGCTAGCTACAACGA ACCCCGTA		TACGGGGT G GCTCCTCA	
1286	CAGTGCGT GGCTAGCTACAACGA CTTGAGGA		TCCTCAAG A ACGCACTG	
1288	GGCAGTGC GGCTAGCTACAACGA GTCTTGAG		CTCAAGAC G GCACTGCC	
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1293	CAGCGGGC GGCTAGCTACAACGA AGTGCGTC		GACGCACT G GCCCGCTG	
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1300	CAGCTCGC GGCTAGCTACAACGA AGCGGGCA		TGCCCGCT G GCGAGCTG	
1304	ACCGCAGC GGCTAGCTACAACGA TCGCAGCG		CGCTGCGA G GCTGCGGT	
1307	GTGACCGC GGCTAGCTACAACGA AGCTCGCA		TGCGAGCT G GCGGTCAC	
1310	GGGGTGAC GGCTAGCTACAACGA CGCAGCTC		GAGCTGCG G GTCACCCC	
1313	GCTGGGGT GGCTAGCTACAACGA GACCGCAG		CTGCGGTC A ACCCCAGC	
1319	CCGGCTGC GGCTAGCTACAACGA TGGGGTGA		TCACCCCA G GCAGCCGG	
1322	ACACCGGC GGCTAGCTACAACGA TGCTGGGG		CCCCAGCA G GCCGGTGT	
1326	ACAGACAC GGCTAGCTACAACGA CGGCTGCT		AGCAGCCG G GTGTCTGT	
1328	GCACAGAC GGCTAGCTACAACGA ACCGGCTG		CAGCCGGT G GTCTGTGC	
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1358	GCCGCCAC GGCTAGCTACAACGA AGAGCCCT		AGGGCTCT G GTGGCGGC	
1361	GGGGCCGC GGCTAGCTACAACGA CACAGAGC		GCTCTGTG G GCGGCCCC	
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1382	GGGTCTGT GGCTAGCTACAACGA GTCCTCCT		AGGAGGAC A ACAGACCC	
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1392	CAGGCGAC GGCTAGCTACAACGA GGGGGTCT		AGACCCCC G GTCGCCTG	
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1402	GCAGCTGC GGCTAGCTACAACGA ACCAGGCG		CGCCTGGT G GCAGCTGC	
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1961	TAGTCCAT GGCTAGCTACAACGA GTTCACAA		TTGTGAAC A ATGGACTA	
1965	GACGTAGT GGCTAGCTACAACGA CCATGTTC		GAACATGG A ACTACGTC	
1968	CACGACGT GGCTAGCTACAACGA AGTCCATG		CATGGACT A ACGTCGTG	
1970	CCCACGAC GGCTAGCTACAACGA GTAGTCCA		TGGACTAC G GTCGTGGG	
1973	GCTCCCAC GGCTAGCTACAACGA GACGTAGT		ACTACGTC G GTGGGAGC	
1979	GTTCTGGC GGCTAGCTACAACGA TCCCACGA		TCGTGGGA G GCCAGAAC	
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1987	TGCGGAAC GGCTAGCTACAACGA GTTCTGGC		GCCAGAAC G GTTCCGCA	
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2011	TGAGACGC GGCTAGCTACAACGA TCGGCCCT		AGGGCCGA G GCGTCTCA	
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2018	CTCGAGGT GGCTAGCTACAACGA GAGACGCT		AGCGTCTC A ACCTCGAG	
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2342	GTAGAGAC GGCTAGCTACAACGA GTGGCTCT		AGAGCCAC G GTCTCTAC	
2348	GTCAAGGT GGCTAGCTACAACGA AGAGACGT		ACGTCTCT A ACCTTGAC	
2354	AGGTCTGT GGCTAGCTACAACGA CAAGGTAG		CTACCTTG A ACAGACCT	
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2372	TGTCGCAT GGCTAGCTACAACGA GTACGGCT		AGCCGTAC A ATGCGACA	
2374	ACTGTCGC GGCTAGCTACAACGA ATGTACGG		CCGTACAT G GCGACAGT	
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2384	TGAGCCAC GGCTAGCTACAACGA GAACTGTC		GACAGTTC G GTGGCTCA	
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2406	CAGCGGGC GGCTAGCTACAACGA TGGTCTCC		GGAGACCA G GCCCGCTG	
2410	CCCTCAGC GGCTAGCTACAACGA GGGCTGGT		ACCAGCCC G GCTGAGGG	
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2420	ACGACGGC GGCTAGCTACAACGA ATCCCTCA		TGAGGGAT G GCCGTCGT	
2423	ATGACGAC GGCTAGCTACAACGA GGCATCCC		GGGATGCC G GTCGTCAT	
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2429	TGCTCGAT GGCTAGCTACAACGA GACGACGG		CCGTCGTC A ATCGAGCA	
2434	AGCTCTGC GGCTAGCTACAACGA TCGATGAC		GTCATCGA G GCAGAGCT	
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3421	AGGGCAGT GGCTAGCTACAACGA GCCGGGTT		AACCCGGC A ACTGCCCT	
3424	CTGAGGGC GGCTAGCTACAACGA AGTGCCGG		CCGGCACT G GCCCTCAG	
3432	CTTGAAGT GGCTAGCTACAACGA CTGAGGGC		GCCCTCAG A ACTTCAAG	
3440	AGGATGGT GGCTAGCTACAACGA CTTGAAGT		ACTTCAAG A ACCATCCT	
3443	TCCAGGAT GGCTAGCTACAACGA GGTCTTGA		TCAAGACC A ATCCTGGA	
3450	CCATCAGT GGCTAGCTACAACGA CCAGGATG		CATCCTGG A ACTGATGG	
3454	GTGGCCAT GGCTAGCTACAACGA CAGTCCAG		CTGGACTG A ATGGCCAC	

3457	CGGGTGGC GGCTAGCTACAACGA CATCAGTC		GACTGATG G GCCACCCG	
3460	GGGCGGGT GGCTAGCTACAACGA GGCCATCA		TGATGGCC A ACCCGCCC	
3464	CTGTGGGC GGCTAGCTACAACGA GGGTGGCC		GGCCACCC G GCCCACAG	
3468	CTGGCTGT GGCTAGCTACAACGA GGGCGGGT		ACCCGCCC A ACAGCCAG	
3471	GGCCTGGC GGCTAGCTACAACGA TGTGGGCG		CGCCCACA G GCCAGGCC	
3476	CTCTCGGC GGCTAGCTACAACGA CTGGCTGT		ACAGCCAG G GCCGAGAG	
3483	GTGTCTGC GGCTAGCTACAACGA TCTCGGCC		GGCCGAGA G GCAGACAC	
3487	GCTGGTGT GGCTAGCTACAACGA CTGCTCTC		GAGAGCAG A ACACCAGC	
3489	CTGCTGGT GGCTAGCTACAACGA GTCTGCTC		GAGCAGAC A ACCAGCAG	
3493	AGGGCTGC GGCTAGCTACAACGA TGGTGTCT		AGACACCA G GCAGCCCT	
3496	GACAGGGC GGCTAGCTACAACGA TGCTGGTG		CACCAGCA G GCCCTGTC	
3501	GGCGTGAC GGCTAGCTACAACGA AGGGCTGC		GCAGCCCT G GTCACGCC	
3504	CCCGGCGT GGCTAGCTACAACGA GACAGGGC		GCCCTGTC A ACGCCGGG	
3506	AGCCCGGC GGCTAGCTACAACGA GTGACAGG		CCTGTCAC G GCCGGGCT	
3511	CGTAGAGC GGCTAGCTACAACGA CCGGCGTG		CACGCCGG G GCTCTACG	
3516	TGGGACGT GGCTAGCTACAACGA AGAGCCCG		CGGGCTCT A ACGTCCCA	
3518	CCTGGGAC GGCTAGCTACAACGA GTAGAGCC		GGCTCTAC G GTCCCAGG	
3535	TGGGCCGC GGCTAGCTACAACGA CCCTCCCT		AGGGAGGG G GCGGCCCA	
3538	GTGTGGGC GGCTAGCTACAACGA CGCCCCTC		GAGGGGCG G GCCCACAC	
3542	CTGGGTGT GGCTAGCTACAACGA GGGCCGCC		GGCGGCCC A ACACCCAG	
3544	GCCTGGGT GGCTAGCTACAACGA GTGGGCCG		CGGCCCAC A ACCCAGGC	
3550	GTGCGGGC GGCTAGCTACAACGA CTGGGTGT		ACACCCAG G GCCCGCAC	
3554	AGCGGTGC GGCTAGCTACAACGA GGGCCTGG		CCAGGCCC G GCACCGCT	
3556	CCAGCGGT GGCTAGCTACAACGA GCGGGCCT		AGGCCCGC A ACCGCTGG	
3559	CTCCCAGC GGCTAGCTACAACGA GGTGCGGG		CCCGCACC G GCTGGGAG	
3566	CCTCAGAC GGCTAGCTACAACGA TCCCAGCG		CGCTGGGA G GTCTGAGG	
3573	ACTCAGGC GGCTAGCTACAACGA CTCAGACT		AGTCTGAG G GCCTGAGT	
3579	ACACTCAC GGCTAGCTACAACGA TCAGGCCT		AGGCCTGA G GTGAGTGT	
3583	CCAAACAC GGCTAGCTACAACGA TCACTCAG		CTGAGTGA G GTGTTTGG	
3585	GGCCAAAC GGCTAGCTACAACGA ACTCACTC		GAGTGAGT G GTTTGGCC	
3590	GCCTCGGC GGCTAGCTACAACGA CAAACACT		AGTGTTTG G GCCGAGGC	

3596	ATGCAGGC GGCTAGCTACAACGA CTCGGCCA		TGGCCGAG G GCCTGCAT	
3600	GGACATGC GGCTAGCTACAACGA AGGCCTCG		CGAGGCCT G GCATGTCC	
3602	CCGGACAT GGCTAGCTACAACGA GCAGGCCT		AGGCCTGC A ATGTCCGG	
3604	AGCCGGAC GGCTAGCTACAACGA ATGCAGGC		GCCTGCAT G GTCCGGCT	
3609	CCTTCAGC GGCTAGCTACAACGA CGGACATG		CATGTCCG G GCTGAAGG	
3616	CACTCAGC GGCTAGCTACAACGA CTTCAGCC		GGCTGAAG G GCTGAGTG	
3621	CCGGACAC GGCTAGCTACAACGA TCAGCCTT		AAGGCTGA G GTGTCCGG	
3623	AGCCGGAC GGCTAGCTACAACGA ACTCAGCC		GGCTGAGT G GTCCGGCT	
3628	GCCTCAGC GGCTAGCTACAACGA CGGACACT		AGTGTCCG G GCTGAGGC	
3634	GCTCAGGC GGCTAGCTACAACGA CTCAGCCG		CGGCTGAG G GCCTGAGC	
3640	ACACTCGC GGCTAGCTACAACGA TCAGGCCT		AGGCCTGA G GCGAGTGT	
3644	CTGGACAC GGCTAGCTACAACGA TCGCTCAG		CTGAGCGA G GTGTCCAG	
3646	GGCTGGAC GGCTAGCTACAACGA ACTCGCTC		GAGCGAGT G GTCCAGCC	
3651	CCCTTGGC GGCTAGCTACAACGA TGGACACT		AGTGTCCA G GCCAAGGG	
3658	CACTCAGC GGCTAGCTACAACGA CCTTGGCT		AGCCAAGG G GCTGAGTG	
3663	CTGGACAC GGCTAGCTACAACGA TCAGCCCT		AGGGCTGA G GTGTCCAG	
3665	TGCTGGAC GGCTAGCTACAACGA ACTCAGCC		GGCTGAGT G GTCCAGCA	
3670	AGGTGTGC GGCTAGCTACAACGA TGGACACT		AGTGTCCA G GCACACCT	
3672	GCAGGTGT GGCTAGCTACAACGA GCTGGACA		TGTCCAGC A ACACCTGC	
3674	CGGCAGGT GGCTAGCTACAACGA GTGCTGGA		TCCAGCAC A ACCTGCCG	
3678	AAGACGGC GGCTAGCTACAACGA AGGTGTGC		GCACACCT G GCCGTCTT	
3681	GTGAAGAC GGCTAGCTACAACGA GGCAGGTG		CACCTGCC G GTCTTCAC	
3687	GGGGAAGT GGCTAGCTACAACGA GAAGACGG		CCGTCTTC A ACTTCCCC	
3695	CAGCCTGT GGCTAGCTACAACGA GGGGAAGT		ACTTCCCC A ACAGGCTG	
3699	GCGCCAGC GGCTAGCTACAACGA CTGTGGGG		CCCCACAG G GCTGGCGC	
3703	CCGAGCGC GGCTAGCTACAACGA CAGCCTGT		ACAGGCTG G GCGCTCGG	
3705	AGCCGAGC GGCTAGCTACAACGA GCCAGCCT		AGGCTGGC G GCTCGGCT	
3710	GGTGGAGC GGCTAGCTACAACGA CGAGCGCC		GGCGCTCG G GCTCCACC	
3715	CCTGGGGT GGCTAGCTACAACGA GGAGCCGA		TCGGCTCC A ACCCCAGG	
3723	AAGCTGGC GGCTAGCTACAACGA CCTGGGGT		ACCCCAGG G GCCAGCTT	
3727	GGAAAAGC GGCTAGCTACAACGA TGGCCCTG		CAGGGCCA G GCTTTTCC	

3737	CTCCTGGT GGCTAGCTACAACGA GAGGAAAA		TTTTCCTC A ACCAGGAG	
3744	AGCCGGGC GGCTAGCTACAACGA TCCTGGTG		CACCAGGA G GCCCGGCT	
3749	GTGGAAGC GGCTAGCTACAACGA CGGGCTCC		GGAGCCCG G GCTTCCAC	
3755	TGGGGAGT GGCTAGCTACAACGA GGAAGCCG		CGGCTTCC A ACTCCCCA	
3762	TCCTATGT GGCTAGCTACAACGA GGGGAGTG		CACTCCCC A ACATAGGA	
3764	ATTCCTAT GGCTAGCTACAACGA GTGGGGAG		CTCCCCAC A ATAGGAAT	
3770	TGGACTAT GGCTAGCTACAACGA TCCTATGT		ACATAGGA A ATAGTCCA	
3773	GGATGGAC GGCTAGCTACAACGA TATTCCTA		TAGGAATA G GTCCATCC	
3777	CTGGGGAT GGCTAGCTACAACGA GGACTATT		AATAGTCC A ATCCCCAG	
3785	TGGCGAAT GGCTAGCTACAACGA CTGGGGAT		ATCCCCAG A ATTCGCCA	
3789	ACAATGGC GGCTAGCTACAACGA GAATCTGG		CCAGATTC G GCCATTGT	
3792	TGAACAAT GGCTAGCTACAACGA GGCGAATC		GATTCGCC A ATTGTTCA	
3795	GGGTGAAC GGCTAGCTACAACGA AATGGCGA		TCGCCATT G GTTCACCC	
3799	CGAGGGGT GGCTAGCTACAACGA GAACAATG		CATTGTTC A ACCCCTCG	
3806	GGCAGGGC GGCTAGCTACAACGA GAGGGGTG		CACCCCTC G GCCCTGCC	
3811	AGGAGGGC GGCTAGCTACAACGA AGGGCGAG		CTCGCCCT G GCCCTCCT	
3821	TGGAAGGC GGCTAGCTACAACGA AAAGGAGG		CCTCCTTT G GCCTTCCA	
3828	GTGGGGGT GGCTAGCTACAACGA GGAAGGCA		TGCCTTCC A ACCCCCAC	
3834	TGGATGGT GGCTAGCTACAACGA GGGGGTGG		CCACCCCC A ACCATCCA	
3837	ACCTGGAT GGCTAGCTACAACGA GGTGGGGG		CCCCCACC A ATCCAGGT	
3843	GTCTCCAC GGCTAGCTACAACGA CTGGATGG		CCATCCAG G GTGGAGAC	
3849	CTCAGGGT GGCTAGCTACAACGA CTCCACCT		AGGTGGAG A ACCCTGAG	
3861	CCCAGGGT GGCTAGCTACAACGA CCTTCTCA		TGAGAAGG A ACCCTGGG	
3870	CCCAGAGC GGCTAGCTACAACGA TCCCAGGG		CCCTGGGA G GCTCTGGG	
3879	CTCCAAAT GGCTAGCTACAACGA TCCCAGAG		CTCTGGGA A ATTTGGAG	
3886	TTGGTCAC GGCTAGCTACAACGA TCCAAATT		AATTTGGA G GTGACCAA	
3889	CCTTTGGT GGCTAGCTACAACGA CACTCCAA		TTGGAGTG A ACCAAAGG	
3896	GGGCACAC GGCTAGCTACAACGA CTTTGGTC		GACCAAAG G GTGTGCCC	
3898	CAGGGCAC GGCTAGCTACAACGA ACCTTTGG		CCAAAGGT G GTGCCCTG	
3900	TACAGGGC GGCTAGCTACAACGA ACACCTTT		AAAGGTGT G GCCCTGTA	
3905	CTGTGTAC GGCTAGCTACAACGA AGGGCACA		TGTGCCCT G GTACACAG	

3907	GCCTGTGT GGCTAGCTACAACGA ACAGGGCA		TGCCCTGT A ACACAGGC	
3909	TCGCCTGT GGCTAGCTACAACGA GTACAGGG		CCCTGTAC A ACAGGCGA	
3913	GTCCTCGC GGCTAGCTACAACGA CTGTGTAC		GTACACAG G GCGAGGAC	
3919	TGCAGGGT GGCTAGCTACAACGA CCTCGCCT		AGGCGAGG A ACCCTGCA	
3924	CCAGGTGC GGCTAGCTACAACGA AGGGTCCT		AGGACCCT G GCACCTGG	
3926	ATCCAGGT GGCTAGCTACAACGA GCAGGGTC		GACCCTGC A ACCTGGAT	
3932	ACCCCCAT GGCTAGCTACAACGA CCAGGTGC		GCACCTGG A ATGGGGGT	
3938	ACAGGGAC GGCTAGCTACAACGA CCCCATCC		GGATGGGG G GTCCCTGT	
3944	TGACCCAC GGCTAGCTACAACGA AGGGACCC		GGGTCCCT G GTGGGTCA	
3948	AATTTGAC GGCTAGCTACAACGA CCACAGGG		CCCTGTGG G GTCAAATT	
3953	CCCCCAAT GGCTAGCTACAACGA TTGACCCA		TGGGTCAA A ATTGGGGG	
3964	CACAGCAC GGCTAGCTACAACGA CTCCCCCC		GGGGGGAG G GTGCTGTG	
3966	CCCACAGC GGCTAGCTACAACGA ACCTCCCC		GGGGAGGT G GCTGTGGG	
3969	ACTCCCAC GGCTAGCTACAACGA AGCACCTC		GAGGTGCT G GTGGGAGT	
3975	TATTTTAC GGCTAGCTACAACGA TCCCACAG		CTGTGGGA G GTAAAATA	
3980	TTCAGTAT GGCTAGCTACAACGA TTTACTCC		GGAGTAAA A ATACTGAA	
3982	TATTCAGT GGCTAGCTACAACGA ATTTTACT		AGTAAAAT A ACTGAATA	
3987	TCATATAT GGCTAGCTACAACGA TCAGTATT		AATACTGA A ATATATGA	
3989	ACTCATAT GGCTAGCTACAACGA ATTCAGTA		TACTGAAT A ATATGAGT	
3991	AAACTCAT GGCTAGCTACAACGA ATATTCAG		CTGAATAT A ATGAGTTT	
3995	TGAAAAAC GGCTAGCTACAACGA TCATATAT		ATATATGA G GTTTTTCA	
4003	TTCAAAAC GGCTAGCTACAACGA TGAAAAAC		GTTTTTCA G GTTTTGAA	

Seq1 = TERT (Homo sapiens telomerase reverse transcriptase (TERT) mRNA, 4015 bp); Nakamura *et al.*, Science 277 (5328), 955-959 (1997)
Cut Site = R/Y (Purine/Pyrimidine)
Stem Length = 8 . Core Sequence = GGCTAGCTACAACGA

Table VII: Anti-TERT HH and G-Cleaver Ribozymes

Alias	Ribozyme Sequence	Length (nt)
HH		
TERT-1051	AGGAGUA CUGAUGAGGCCGUUAGGCCGAA AGGAAGU	36
TERT-1053	UGAGGAG CUGAUGAGGCCGUUAGGCCGAA AGAGGAA	36
TERT-1918	UGAAGCG CUGAUGAGGCCGUUAGGCCGAA AGUCUGG	36
TERT-2383	GAGCCAC CUGAUGAGGCCGUUAGGCCGAA AACUGUC	36
TERT-2485	UGAAGCG CUGAUGAGGCCGUUAGGCCGAA AGGAAGA	36
TERT-2566	GCGUGGA CUGAUGAGGCCGUUAGGCCGAA AGGAUGG	36
TERT-3181	AGUAGCA CUGAUGAGGCCGUUAGGCCGAA AGGGAGG	36
TERT-3691	CUGUGGG CUGAUGAGGCCGUUAGGCCGAA AAGUGAA	36
TERT-3758	AUGUGGG CUGAUGAGGCCGUUAGGCCGAA AGUGGAA	36
TERT-3794	GGUGAAC CUGAUGAGGCCGUUAGGCCGAA AUGGCGA	36
G-Cleaver		
TERT-757	UUGGG UGAUGGCAUGCACUAUGCGCG AACGGCAGAC	36
TERT-2353	UCUGU UGAUGGCAUGCACUAUGCGCG AAGGUAGAGA	36
TERT-3795	GUGAA UGAUGGCAUGCACUAUGCGCG AAUGGCGAAU	36

CLAIMS

1. An enzymatic nucleic acid molecule which specifically cleaves RNA derived from a TERT gene, wherein said enzymatic nucleic acid molecule comprises any of the ribozyme sequences defined in tables III, IV, V and VII.

2. An enzymatic nucleic acid molecule which specifically cleaves RNA derived from a TERT gene, wherein said enzymatic nucleic acid molecule is a DNA enzyme.

3. An enzymatic nucleic acid molecule of claim 2, wherein said enzymatic nucleic acid molecule comprises any of the DNAzyme sequences defined in table VI.

4. An enzymatic nucleic acid molecule which specifically cleaves RNA derived from a TERT gene, wherein said enzymatic nucleic acid molecule comprises sequences that are complementary to any of substrate sequences defined in tables III-VI.

5. An antisense nucleic acid molecule comprising sequence complementary to any of substrate sequence in Tables III-VI.

6. The enzymatic nucleic acid molecule of any of claims 1, 2 and 4, wherein said enzymatic nucleic acid is chemically synthesized.

7. The enzymatic nucleic acid molecule of any of claims 1, 2 and 4, wherein said enzymatic nucleic acid comprises at least one 2'-sugar modification.

8. The enzymatic nucleic acid molecule of any of claims 1, 2 and 4, wherein said enzymatic nucleic acid comprises at least one nucleic acid base modification.

9. The enzymatic nucleic acid molecule of any of claims 1, 2 and 4, wherein said enzymatic nucleic acid comprises at least one phosphate backbone modification.

10. The antisense nucleic acid molecule of claim 5, wherein said antisense nucleic acid is chemically synthesized.

11. The antisense nucleic acid molecule of claim 5, wherein said antisense nucleic acid comprises at least one 2'-sugar modification.

12. The antisense nucleic acid molecule of claim 5, wherein said antisense nucleic acid comprises at least one nucleic acid base modification.

13. The antisense nucleic acid molecule of claim 5, wherein said antisense nucleic acid comprises at least one phosphate backbone modification.

14. A mammalian cell including the enzymatic nucleic acid molecule of any of claims 1, 2, 4 and 5, wherein said mammalian cell is not a living human.

15. The mammalian cell of claim 14, wherein said mammalian cell is a human cell.

16. A method of inhibiting telomerase enzyme activity in a cell, comprising the step of contacting said cell with the enzymatic nucleic acid molecule of any of claims 1, 2 and 4, under conditions suitable for said inhibition.

17. A method of inhibiting telomerase enzyme activity in a cell, comprising the step of contacting said cell with the antisense nucleic acid molecule of claim 5, under conditions suitable for said inhibition.

18. A method of treatment of a patient having a condition associated with the level of TERT, comprising contacting cells of said patient with the enzymatic nucleic acid molecule of any of claims 1, 2, and 4, under conditions suitable for said treatment.

19. The method of claim 18 further comprising the use of one or more drug therapies under conditions suitable for said treatment.

20. A method of treatment of a patient having a condition associated with the level of TERT, comprising contacting cells of said patient with the antisense nucleic acid molecule of claim 5, under conditions suitable for said treatment.

21. The method of claim 20 further comprising the use of one or more drug therapies under conditions suitable for said treatment.

22. A method of cleaving RNA encoded by a TERT gene, comprising, contacting the enzymatic nucleic acid molecule of any of claims 1, 2 and 4 with said RNA under conditions suitable for the cleavage of said RNA.

23. The method of claim 22, wherein said cleavage is carried out in the presence of a divalent cation.

24. The method of claim 23, wherein said divalent cation is Mg^{2+}.

25. The enzymatic nucleic acid molecule of claims 1, wherein said enzymatic nucleic acid molecule comprises any of sequences of table III.

26. The enzymatic nucleic acid molecule of claims 1, wherein said enzymatic nucleic acid molecule comprises any of sequences of table IV.

27. The enzymatic nucleic acid molecule of claims 1, wherein said enzymatic nucleic acid molecule comprises any of sequences of table V.

28. The enzymatic nucleic acid molecule of claims 1, wherein said enzymatic nucleic acid molecule comprises any of sequences of table VII.

29. The enzymatic nucleic acid molecule of any of claims 1, 2 and 4, wherein said enzymatic nucleic acid comprises a cap structure, wherein the cap structure is at the 5'-end or 3'-end or both the 5'-end and the 3'-end.

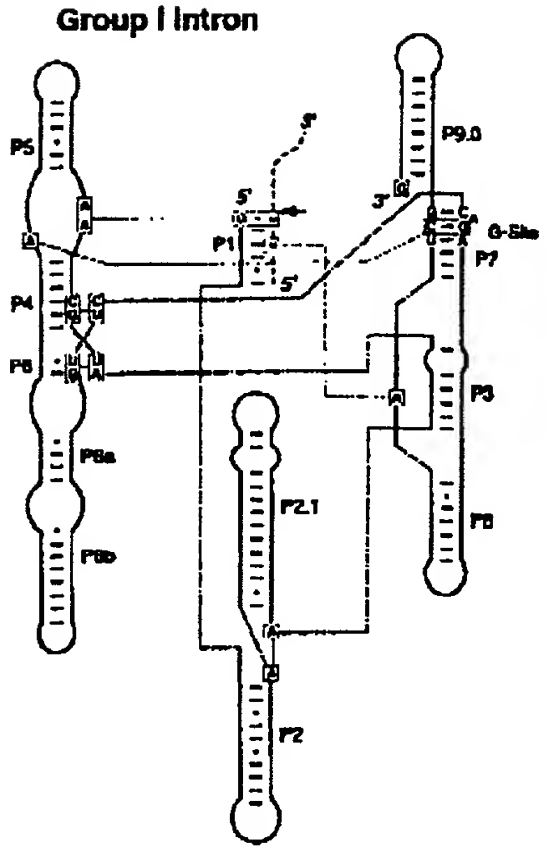
30. The antisense nucleic acid molecule of claim 5, wherein said antisense nucleic acid comprises a cap structure, wherein the cap structure is at the 5'-end or 3'-end or both the 5'-end and the 3'-end.

Abstract Of The Disclosure

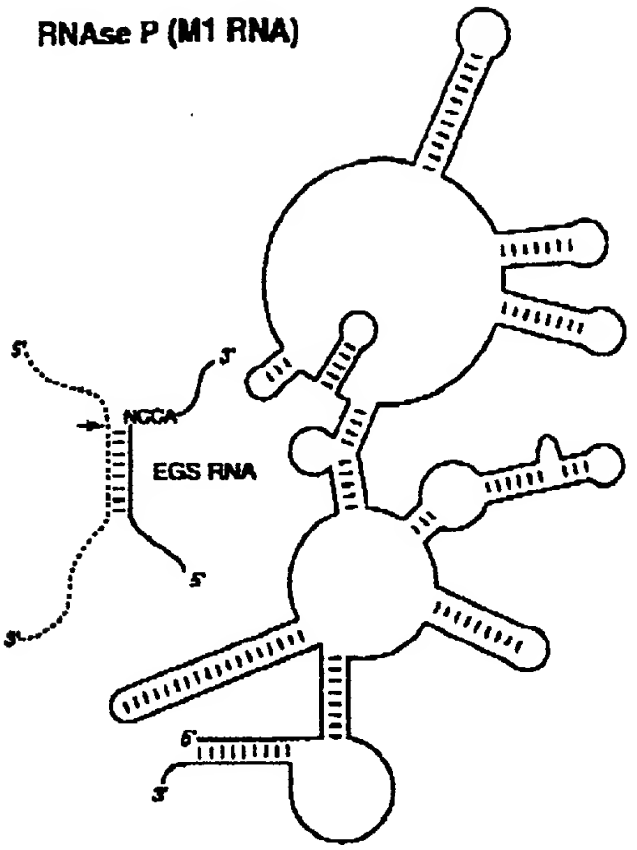
Nucleic acid molecule which modulates the synthesis, expression and/or stability of an RNA encoding one or more protein subunit of telomerase enzyme.

Figure 1: Ribozyme Motifs

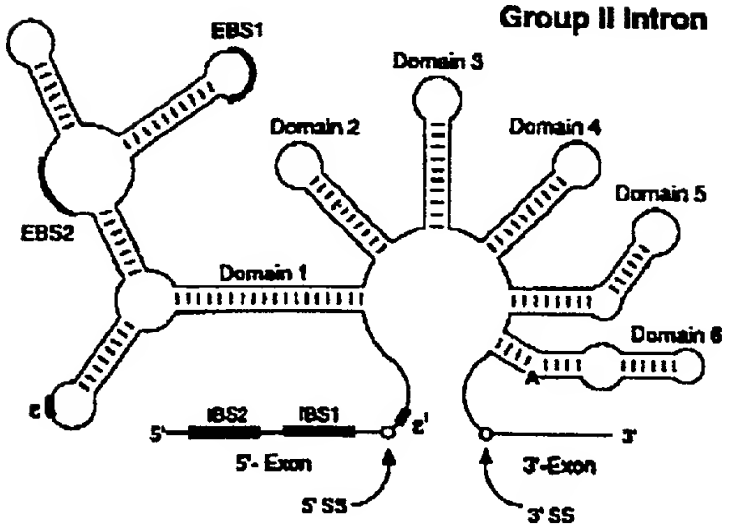
Group I Intron



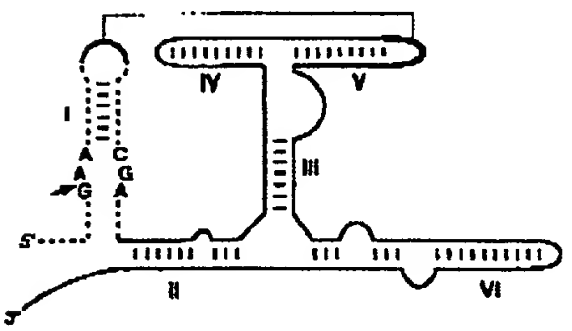
RNAse P (M1 RNA)



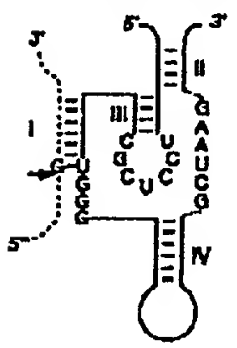
Group II Intron



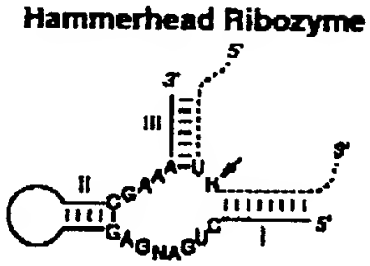
VS RNA



HDV Ribozyme



Hammerhead Ribozyme



Hairpin Ribozyme

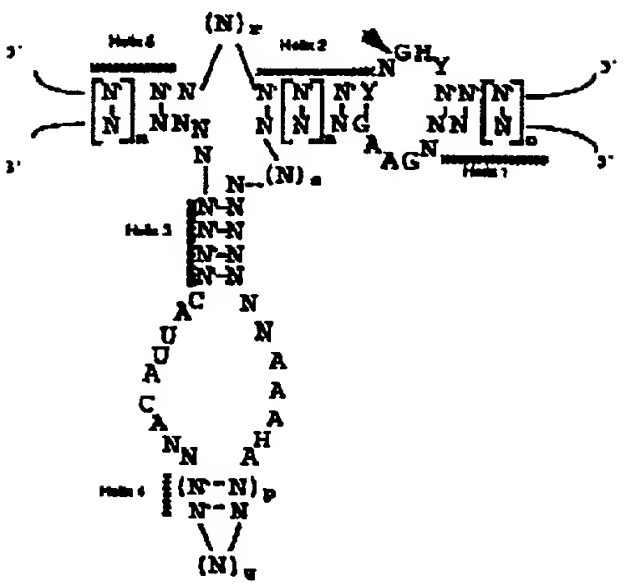


Figure 2: Examples of Nuclease Stable Ribozyme Motifs

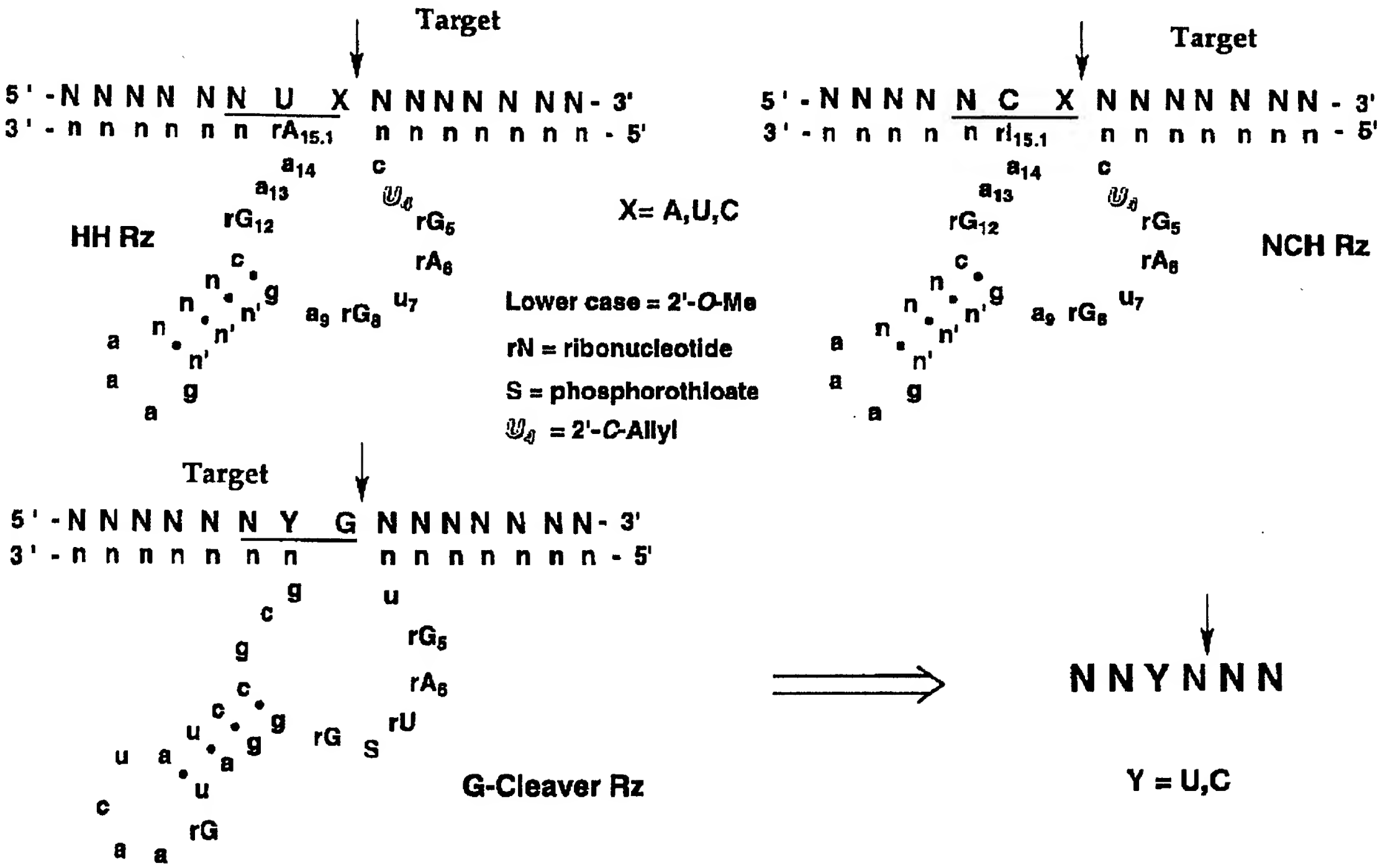


Figure 3. 2'-*O*-Me substituted Amberzyme Enzymatic Nucleic Acid Motif

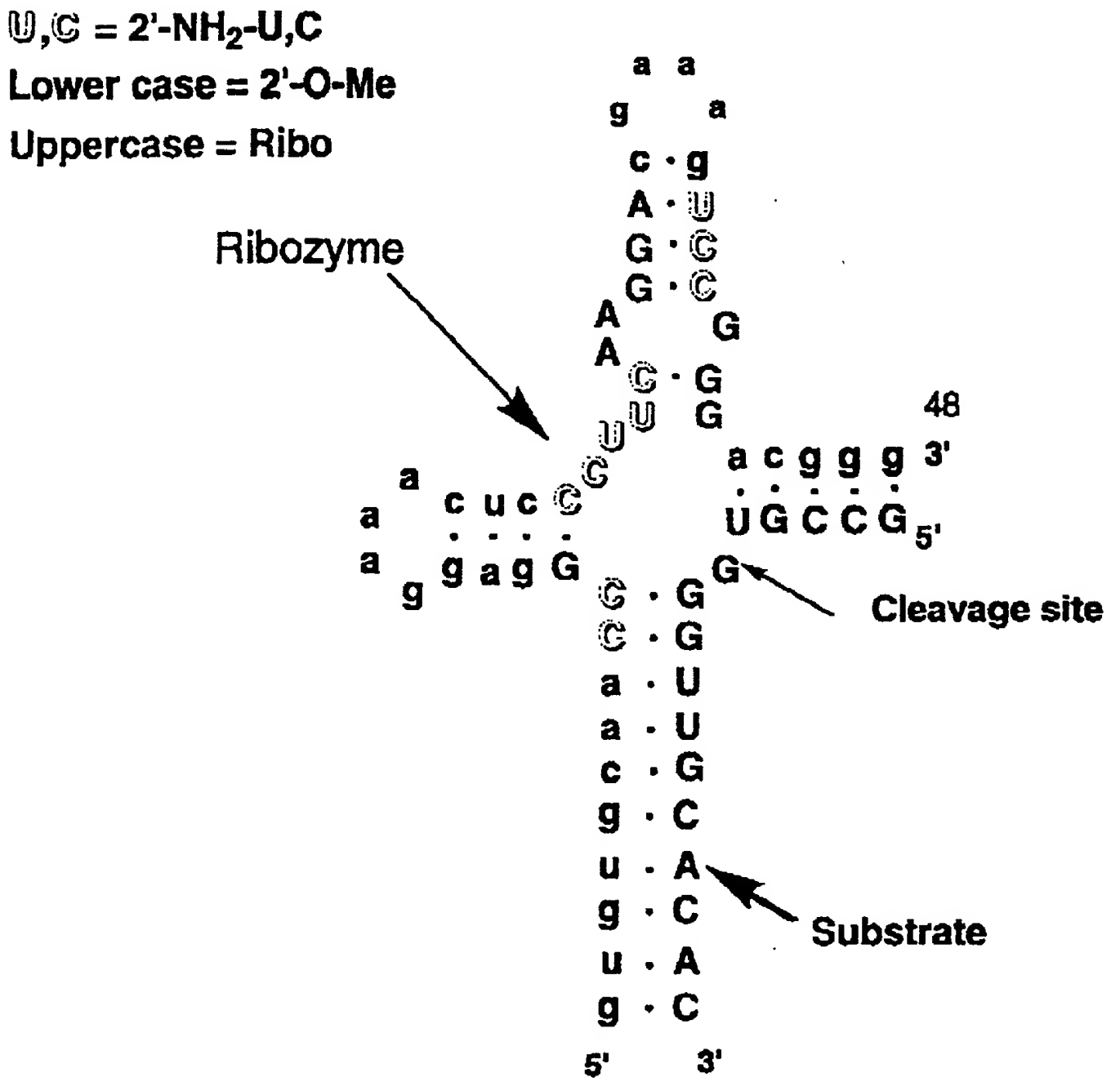
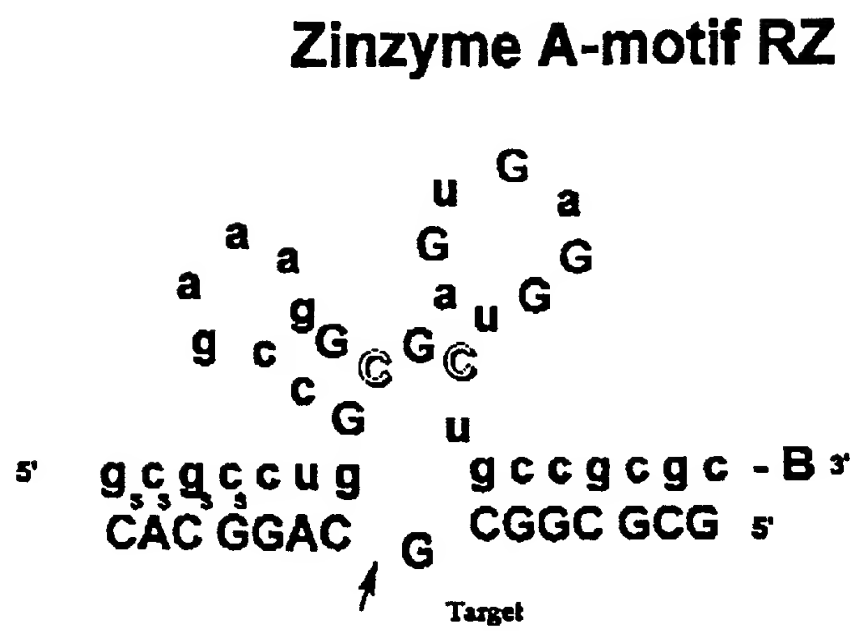


Figure 4: Zinzyme Motif



Legend

Uppercase indicates natural ribo residues

Ⓒ Indicates 2' - d-NH_2-C

Lowercase: 2'-O- Me

Subscript $_S$ indicates phosphothioate linkage

B: 3'-3' abasic moiety

The GAAA tetraloop can be replaced by 18 atom polyethylene glycol (Spacer)
All ribo G's can be replaced with 2'-O-*methyl* G